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(54) Title: CHIRAL CATALYSTS, CATALYTIC OXIDATION AND DISPROPORTIONATION REACTIONS, AND METHODS OF PRODUCING EPOXYCHROMANS AND TAXOL

(I)

(57) Abstract

Chiral catalysts for enantioselectively epoxidizing a prochiral olefin and for enantioselectively oxidizing a prochiral sulfide are disclosed, together with methods f using such catalysts. In accordance with ne aspect of the invention, the catalyst is a salen derivative which has general structure (I). In accordance with another aspect of the present invention is a method of producing an epoxychroman using a chiral catalyst. In accordance with this method, a chromene derivative, an xygen atom source, and a chiral catalyst are reacted under such conditions and for such time as is needed to epoxidize said chromene derivative. In accordance with yet another aspect f this invention is a method of enantioselectively epoxidizing a cis-cinnamate derivative to make taxol r an analog thereof. In accordance with another aspect a method of disproportionation of hydrogen peroxide using the catalysts of the present invention is discl sed.

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CHIRAL CATALYSTS, CATALYTIC OXIDATION AND DISPROPORTIONATION REACTIONS, AND METHODS OF PRODUCING EPOXYCHROMANS AND TAXOL

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STATEMENT OF GOVERNMENT INTEREST

CROSS-REFERENCE TO RELATED APPLICATION

The present application is a continuation-in-part of U.S. Patent Application No. 809,446 filed December 16, 1991 which application was in turn a continuation-in-part of U.S. Patent Application No. 749,460 filed August 26, 1991, and of U.S. Patent Application No. 673,208 filed March 21, 1991 which application was in turn a continuation-in-part of U.S. Patent Application No. 496,992 filed March 21, 1990 and since abandoned.

BACKGROUND OF THE INVENTION

Chiral Catalysts and Catalysis

The present invention relates to the field of asymmetric catalysis. More particularly, the invention relates to the field of organometallic catalysts useful for enantioselectively epoxidizing prochiral olefins.

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Several advances in catalysis of asymmetric group transfer have occurred in recent years. One such advance has been the discovery by K.B. Sharpless et al. of the epoxidation of allylic alcohols which provides access to enantiomerically pure synthetic building blocks. Unfortunately, Sharpless

5   catalysis requires the presence of a specific functional group, namely an allylic alcohol, on the olefin to be epoxidized. Naturally, this requirement severely limits the variety of olefins which can be so epoxidized.

Some success has been achieved in asymmetric catalysis of unfunctionalized olefins. For example, K.B. Sharpless reported in 1988 that

10   certain cinchona alkaloid derivatives were effective ligands in the osmium-catalyzed asymmetric dihydroxylation of trans-stilbene and various other olefins. This method provides a practical route to certain chiral diols, although cis olefins afford poor results.

Aside from the catalysts disclosed herein, it is believed that

15   there currently exists no practical catalytic method for the asymmetric epoxidation of unfunctionalized olefins. Some progress has been made in this area through the use of chiral porphyrin complexes. In particular, J.T. Groves et al. reported in 1983 the asymmetric epoxidation of styrene by a chiral iron porphyrin catalyst. Unfortunately, the Groves system suffers several

20   disadvantages, namely, the porphyrin catalyst is relatively difficult to prepare, oxidant proceeds to low substrate conversion, is limited to styrene derivatives, and achieves enantiomeric excess (ee) values of less than about 50 percent.

Epoxychroman Synthesis

Given the broad synthetic utility of epoxides, a simple, reliable,

25   and practical procedure for asymmetric epoxidation of simple olefins is clearly desirable. One class of chiral epoxide with synthetic utility is the group of compounds generally known as epoxychromans, or epoxides of derivatives of chromene. For example, the epoxide of 6-cyano-2,2-dimethylchromene has been found to be useful in the synthesis of a compound known as cromakalim.

30   Two variations of cromakalim are shown in FIGURES 12 and 13. Both of

these are believed to be potassium channel activators and have shown considerable promise as antihypertensive drugs.

As can be seen in FIGURES 12 and 13, the cromakalim compounds have two enantiomers. It is currently believed that only one of these enantiomers, namely the 3S, 4R enantiomer, possesses the antihypertensive activity. Consequently, a method of making a more enantiomerically pure epoxide of the precursor chromene derivative is highly desirable.

Taxol Synthesis

Taxol has emerged as a promising anti-cancer drug in preliminary clinical trials. However, taxol is a highly complex molecule which has not been fully synthesized and remains in short supply. Taxol may be considered to have two basic structural units, an N-benzoyl-3-phenyl-isoserine side chain and a highly functionalized diterpene nucleus. The tetracyclic ring structure of the nucleus represents by far the greater synthetic challenge, one that has as yet not been met despite the concerted efforts of several leading laboratories.

Consequently, a number of research groups are seeking semisynthetic routes of making taxol or analogs with taxol-like activity. Some of the new strategies involve side-chain synthesis and linkage to a naturally derived diterpene nucleus, or taxol congener.

A ready source of the taxol congener 10-deacetyl baccatin III (10-DB III) has been found. Chauviere, G., Guenard, D.; Picot, F.; Senilh, V.; Potier, P. C.R.: Seances Acad. Sci., Ser. 2, 293: 501-03, 1981. Denis et al. (J. Amer. Chem. Soc. 110:5417, 1988) developed a method of converting 10-DB III to taxol which utilizes, for the taxol C13 side chain, the protected form (2R,3S)-N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine. Denis, J.-N.; Greene, A.E.; Serra, A.A.; Luche, M.-J. J. Org. Chem. 51: 46-50, 1986.

A more efficient method of synthesizing an optically pure C13 side chain of taxol is desirable.

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Chiral Catalysts and Oxidation of Sulfides

The present invention also relates to the field of organometallic catalysts useful for enantioselectively oxidizing sulfides to sulfoxides. Given the broad synthetic utility of sulfoxides, a simple, reliable, and practical procedure for asymmetric oxidation of sulfides is clearly desirable.

Asymmetric sulfide oxidation and olefin epoxidation strategies utilizing chiral oxaziridine derivatives have been developed with good to excellent success by Davis et al. Enantioselective catalysis of these reactions (and of asymmetric stoichiometric epoxidation) constitutes among the most interesting challenges in modern synthetic chemistry. To date, the only well-established and broadly successful methods for both these processes employ closely related Ti-tartrate-based catalysts with alkyl hydroperoxides as the terminal oxidant. Also, several chiral porphyrin complexes have been reported to catalyze both types of oxidation processes with modest selectivity using iodosylarenes as terminal oxidants.

Catalytic Disproportionation of Hydrogen Peroxide

The enzyme catalase, which occurs in blood and a variety of tissues decomposes hydrogen peroxide into oxygen gas and water very rapidly. This catalytic disproportionation of hydrogen peroxide (also known as the catalatic reaction) protects aerobic cells from oxidative stress and therefore is a biologically important process. Thus, it is desirable to find compounds which can function like catalase.

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SUMMARY OF THE INVENTION

Briefly stated, the present invention is a chiral catalyst as well as a method of using said catalyst for enantioselectively epoxidizing a prochiral olefin.

In accordance with a first aspect of the invention, the chiral catalyst has the following structure:
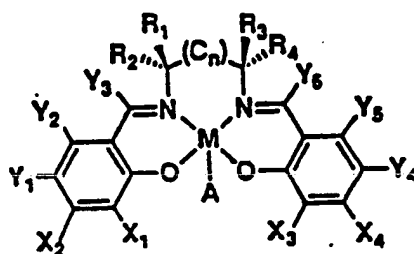
wherein M is a transition metal ion, A is an anion, and n is either 0, 1, or 2. At least one of X1 or X2 is selected from the group consisting of silyls, aryls, secondary alkyls and tertiary alkyls; and at least one of X3 or X4 is selected from the same group. Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryl groups, silyl groups, and alkyl groups bearing hetero-atoms such as alkoxy and halide. Also, at least one of R1, R2, R3 and R4 is selected from a first group consisting of H, CH_3, C_2H_5, and primary alkyls. Furthermore, if R1 is selected from said first group, then R2 and R3 are selected from a second group consisting of aryl groups, heteroatom-bearing aromatic groups, secondary alkyls and tertiary alkyls. If R2 is selected from said first group, then R1 and R4 are selected from said second group. If R3 is selected from said first group, then R1 and R4 are selected from said second group. If R4 is selected from said first group, then R2 and R3 are selected from said second group.

In accordance with a second aspect of the invention, the chiral catalyst has the following structure:

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wherein M is a transition metal ion and A is an anion; where at least one of
$X1$ or $X2$ is selected from the group consisting of aryls, primary alkyls,
secondary alkyls, tertiary alkyls, and hetero atoms; where at least one of $X3$ or
$X4$ is selected from the group consisting of aryls, primary alkyls, secondary
5   alkyls, tertiary alkyls, and hetero atoms; and where $Y1$, $Y2$, $Y3$, $Y4$, $Y5$, $Y6$,
$Z1$, $Z2$, $Z3$, $Z4$, $Z5$, $Z6$, $Z7$, $Z8$, $Z9$, $Z10$, $Z11$, and $Z12$ are independently
selected from the group consisting of hydrogen, halides, alkyls, aryls, and
alkyl groups bearing hetero atoms.

        In accordance with a third aspect of the invention, the chiral
10   catalyst has the following structure:
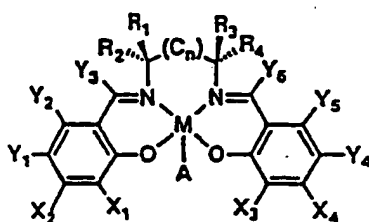
where M is a transition metal ion and A is an anion; where n is either 0, 1, or
2; where at least one of $X1$ or $X2$ is selected from the group consisting of
aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;
15   where at least one of $X3$ or $X4$ is selected from the group consisting of aryls,
primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where at

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least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where Y3 and Y6 are

5 independently selected from the group consisting of hydrogen and primary alkyl groups; where either one or two of R1, R2, R3 and R4 is hydrogen; where, if R1 is hydrogen, then R3 is a primary alkyl; where, if R2 is hydrogen, then R4 is a primary alkyl; where, if R3 is hydrogen, then R1 is a primary alkyl; and where, if R4 is hydrogen, then R2 is a primary alkyl.
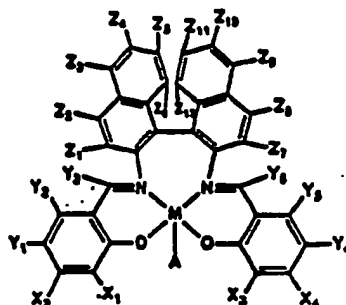
10   In accordance with a fourth aspect of the invention, chiral catalyst has the following structure:

where M is a transition metal ion and A is an anion; where n is either 3, 4, 5 or 6; where at least one of X1 or X2 is selected from the group consisting of

15 aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where at least one

20 of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; where Y3, and Y6 are independently selected from the group consisting of hydrogen and primary

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alkyl groups; where R1 and R4 are _trans_ to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen; and where the carbons in the (C)$_n$ portion have substituents selected from the group consisting of hydrogen, alkyl, aryl, and heteroatoms.

In accordance with the method aspect of the invention, a prochiral olefin, an oxygen atom source, and the chiral catalyst of one of the four aspects of the invention are reacted under such conditions and for such time as is needed to epoxidize said olefin.

In accordance with an alternate method aspect of this invention, a pyridine-N-oxide derivative is used. Preferably, 4-phenylpyridine-N-oxide or 4-t-butylpyridine-N-oxide is used. More preferably, 4-phenylpyridine-N-oxide is used.

The present invention of chiral catalysts and catalysis has provided certain advantages. First, the catalysts of the present invention provide a means for catalyzing the enantioselective epoxidation of mono, di, and tri-substituted olefins without the need for a specialized functional group on the olefin to interact with the catalyst. In other words, the catalysts of the present invention are particularly suited for catalyzing the asymmetric epoxidation of unfunctionalized olefins. This is in contrast to the prior art catalysts, such as the Sharpless catalyst, referred to above.

Second, the preferred catalysts of the invention show remarkable enantioselectivity in catalyzing the epoxidation of _cis_, disubstituted olefins. See Example 1 below, where an ee of 85% was obtained with _cis_-ß-methylstyrene when catalyzed with the most preferred embodiment of the first aspect. See also, the ee values for Example 12 which uses the most preferred catalyst of the fourth aspect of the present invention. As noted above, prior art catalysts have not provided ee values over 40% for _cis_, disubstituted olefins.

Third, the catalysts of the present invention are relatively easy to synthesize, particularly as compared to the porphyrin systems disclosed in the prior art.

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Briefly stated, yet another embodiment of the present invention is a method of producing an epoxychroman using a chiral catalyst. In accordance with this method, a chromene derivative, an oxygen atom source, and a chiral catalyst from those described below are reacted under such condi-

5   tions and for such time as is needed to epoxidize said chromene derivative.

The chromene derivative used in the present method has the following structure:
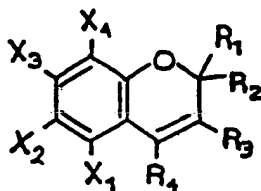
wherein R1, R2, R3, R4, X1, X2, X3, and X4 are each selected from the

10   group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms, and wherein no more than one of R1 and R2 are hydrogen.

The enantioselective method of producing an epoxychroman has provided certain advantages. First, the preferred catalysts of the invention

15   show remarkable enantioselectivity in catalyzing the epoxidation of chromene derivatives. See Example 17 below, where an ee of 97% was obtained with the 6-cyano-2,2-dimethylchromene and the most preferred catalyst shown below. As noted above, prior art catalysts have not provided ee values over 40% for cis, disubstituted olefins.

20   Second, the present invention provides an effective and concise route to epoxychromans with very high enantioselectivity. Enantiomerically enriched epoxychromans are valuable intermediates for the synthesis of chiral 3,4-disubstituted chromans.

Third, the method is effective with a wide variety of substituted

25   chromene derivatives.

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Fourth, the catalysts of the present invention are relatively easy to synthesize, particularly as compared to the porphyrin systems disclosed in the prior art.

Yet another embodiment of the present invention is the method of enantioselectively producing a cis-epoxide of a cinnamate derivative using a chiral catalyst. In accordance with this method, a cis-cinnamate derivative, an oxygen atom source, and a chiral catalyst selected from those described below are reacted under such conditions and for such time as needed to epoxidize said cis-cinnamate derivative. Even more preferably, the reaction takes place in the presence of a pyridine-N-oxide derivative.

The cis-cinnamate derivative used in the present method has the following structure:
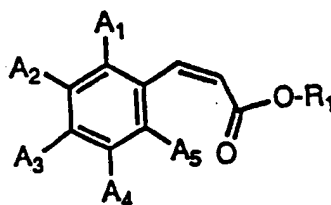
wherein A1-A5 are selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl, alkoxy groups, F, Cl, Br, I, and amines.

Still another embodiment of the present invention is the method of making a side chain of taxol or an analog thereof using a chiral catalyst. In accordance with this method, a cis-cinnamate derivative, an oxygen atom source, and a chiral catalyst selected from those described below are reacted under such conditions and for such time as needed to enantioselectively epoxidize said cis-cinnamate derivative. Even more preferably, the reaction takes place in the presence of a pyridine-N-oxide derivative. The cis-cinnamate derivative has the same structure as shown above.

The epoxide of cis-epoxide of the cinnamate derivative is then regioselectively opened (i.e., preferentially breaking one particular oxygen bond) to produce 3-phenyl isoserinamide derivative. This 3-phenyl

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isoserinamide derivative is hydrolyzed to produce a 3-phenyl-isoserine derivative, which in turn is reacted with benzoyl chloride to form N-benzoyl-3-phenyl-isoserine derivative.

5   In yet another embodiment of this invention, taxol is synthesized using a chiral catalyst. In accordance with this method, an ethyl phenylpropiolate is partially hydrogenated to produce a cis-ethyl cinnamate. Then, the cis-ethyl cinnamate, an oxygen atom source, and a chiral catalyst selected from those described below are reacted under such conditions and for such time as needed to enantioselectively epoxidize said cis-ethyl cinnamate.

10   Even more preferably, the reaction takes place in the presence of a pyridine-N-oxide derivative.

       The epoxide of cis-epoxide of the ethyl cinnamate is then regioselectively opened to produce 3-phenyl isoserinamide. This 3-phenyl isoserinamide is hydrolyzed to produce 3-phenyl-isoserine, which in turn is

15   reacted with benzoyl chloride to form N-benzoyl-3-phenyl-isoserine. Next, the N-benzoyl-3-phenyl-isoserine is reacted with 1-chloroethyl ether and a tertiary amine in methylene chloride to form N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine. Then, N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine is reacted with the alcohol shown below:
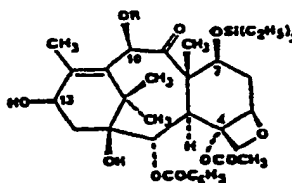
20   This resulting intermediate is converted to taxol by hydrolytically removing the 1-ethoxyethyl and R4 chains.

       The present method of enantioselectively synthesizing the side chain of taxol has certain advantages. The preferred catalysts of the invention show remarkable enantioselectivity in catalyzing the epoxidation of cis-

25   cinnamate derivatives. The synthesis may begin with relatively inexpensive

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ethyl phenylpropiolate. In particular, the addition of a pyridine-N-oxide derivative also increases the specificity and completion of the epoxidation.

Briefly stated, yet another embodiment of the present invention is a method of enantioselectively oxidizing sulfides using a chiral catalyst. In accordance with this method a sulfide, an oxygen atom source, and a chiral catalyst from those described below are reacted under such conditions and for such time as is needed to oxidize said sulfide. Preferably, the sulfide has the formula R1-S-R2 wherein R1 is any aromatic group and R2 is any alkyl group. Preferably, a cosolvent such as tetrahydrofuran, acetone or acetronitrile is employed. Also preferably, the oxygen atom source is either hydrogen peroxide or iodosylbenzene.

Still another embodiment of the invention is a method of catalytic disproportionation of hydrogen peroxide using a catalyst of the present invention. In accordance with this method, hydrogen peroxide and a catalyst selected from those described below are reacted under such conditions and for such time as is needed to disproportionate the hydrogen peroxide to dioxygen and water. Preferably, the catalyst is a monometallic (salen)Mn complex. Also preferably, the catalyst is mixed with a solvent such as EtOH, acetone, CH_2Cl_2, or H_2O.

The present invention, together with attendant objects and advantages, will be best understood with reference to the detailed description below read in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the generalized 2-dimensional structure of a catalyst of the first aspect of the present invention.

FIGURE 2 shows the 2-dimensional structure of the most preferred catalyst of the first aspect of the present invention.

FIGURE 3 shows the generalized 2-dimensional structure of the catalyst of the second aspect of the present invention.

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FIGURE 4 is a computer generated 3-dimensional view of the most preferred catalyst of the present invention in its proposed oxo-intermediate state.

FIGURES 5A-5C are views similar to FIGURE 4 illustrating the steric hindrance believed to be responsible for the high enantioselectivity observed in the epoxidation of one of the preferred substrates by the preferred catalysts of the present invention.

FIGURE 6 shows the generalized 2-dimensional structure of the catalyst of the third aspect of the present invention.

FIGURE 7 shows the generalized 2-dimensional structure of a the catalyst of the fourth aspect of the present invention.

FIGURE 8 shows the 2-dimensional structure of the preferred catalyst of the fourth aspect of the present invention.

FIGURE 9 is a 2-dimensional representation of the theorized favored approach of a prochiral olefin to a preferred catalyst of the first aspect of the invention.

FIGURE 10 is a 2-dimensional representation of the theorized favored approach of a prochiral olefin to a preferred catalyst of the second aspect of the invention.

FIGURE 11 shows 2-dimensional structures for various embodiments of the present invention with the numbering system used in Examples 8-16.

FIGURE 12 shows the structure of the chromene derivatives used in the present method.

FIGURE 13 shows the structure of the 3S, 4R enantiomer of one cromakalim compound.

FIGURE 14 shows the structure of the 3S, 4R enantiomer of another cromakalim compound.

FIGURE 15 shows the structure of 6-cyano-2,2-dimethyl-3,4-epoxychroman.

FIGURE 16 shows the structure of taxol.

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FIGURE 17 shows the structure of the cinnamate derivatives used in the present method.

FIGURE 18 shows the generalized structure and analogs of the 3S, 4R enantiomer of the C-13 side chain of taxol.

5   FIGURE 19 shows the structure of a preferred chiral catalyst used in asymmetric sulfide oxidation.

FIGURE 20 shows the structure of another preferred chiral catalyst used in asymmetric sulfide oxidation.

FIGURE 21 shows the face selectivity in sulfide oxidation

10   reactions.

FIGURE 22 shows the generalized structure of a preferred catalyst used in catalytic disproportionation of hydrogen peroxide.

FIGURE 23 shows the generalized structure of another preferred catalyst used in catalytic disproportionation of hydrogen peroxide.

15   ## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As noted above, the present invention is a chiral catalyst as well as methods of using said those catalysts for enantioselectively epoxidizing prochiral olefins, chromene derivatives and cis-cinnamate derivatives.

The entire disclosures of U.S. Patent Application No. 809,446

20   filed December 16, 1991 and U.S. Patent Application No. 749,460 filed August 26, 1991, and of U.S. Patent Application No. 673,208 filed March 21, 1991 which application was in turn a continuation-in-part of U.S. Patent Application No. 496,992 filed March 21, 1990 are incorporated herein by reference.

25   ### The First Catalyst of the Invention

FIGURE 1 shows the structure of the first aspect of the present invention preferred chiral catalyst.

The preferred catalysts of the present invention are salen derivative-based complexes of a metal ion. The term "salen" is used herein to

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refer to those ligands typically formed through a condensation reaction of two molecules of a salicylaldehyde derivative with one molecule of a diamine derivative. While salen ligands are formed from ethylenediamine derivatives, propyl and butyl diamines may also be used to give analogous salpn and salbn derivatives. Salen derivatives are preferred and their general structure is shown in FIGURE 1. A salen derivative where n is 0 is shown in FIGURE 2.

As seen in FIGURE 1, the two nitrogens and the two oxygens are oriented toward the center of the salen ligand and thus provide a complexing site for the transition metal ion M. Preferably, this metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os. More preferably, the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, and Co. Most preferably, the metal ion is Mn.

The selection of the anion, A, is not seen to be critical to the performance of the catalyst. Preferably, the anion is selected from the group consisting of PF_6, $(aryl)_4$, BF_4, $B(aryl)_4$, halide, acetate, triflate, tosylate, with halide or PF_6 being more preferred, and chloride being most preferred.

FIGURE 1 also shows the many sites available for substitution on the salen ligand. Of these sites, it is believed that R1, R2, R3, R4, and X1, X2, X3, X4, Y3 and Y6 are the most important in this first catalyst.

According to the first aspect of the invention, at least one of the X1 and X2 sites, and at least one of the X3 and X4 sites include a substituent selected from the group consisting of secondary or tertiary alkyl groups, aryl groups, silyl groups, and alkyl groups bearing heteroatom substituents such as alkoxy or halide. For reasons to be discussed below, these will be referred to as "blocking" substituents. Preferably, it is the X1 and X3 sites which bear one of these blocking substituents. More preferably, X1 and X3 bear the same substituent, which substituent is most preferably a tertiary alkyl group, such as tertiary butyl. Preferably, when X1 and X3 bear the blocking substituent, then X2 and X4 can be selected from a group of non-blocking substituents such as H, CH_3, C_2H_5, and primary alkyls, most preferably, H. Alternatively, either

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three or four of X1, X2, X3, and X4 can be selected from the group of blocking substituents.

According to this first aspect of the invention, at least one and no more than two of R1, R2, R3 and R4 are selected from a group consisting of H, CH_3, C_2H_5, and primary alkyls. For convenience, and consistent with the present theory to be discussed below, this group will be referred to as the non-blocking group. If R1 is selected from the non-blocking group, then R2 and R3 are selected from the blocking group. If R2 is selected from the non-blocking group, then R1 and R4 are selected from the blocking group. Likewise, if R3 is selected from the non-blocking group, then R1 and R4 are selected from the blocking group. Finally, if R4 is selected from the non-blocking group, then R2 and R3 are selected from the blocking group.

Stated in other terms, this first aspect of the invention requires that, of the four sites available for substitution on the two carbon atoms adjacent to nitrogen, either one or two of these will include a substituent from the non-blocking group. The invention also requires that the remaining sites include a substituent from the blocking group. In addition, it is a requirement that there not be two non-blocking substituents on the same carbon, and that there not be two non-blocking substituents on the same side on the two different carbons, i.e. not _cis_ across the nitrogen.

Stated in yet another way, if there is only one non-blocking substituent, that non-blocking substituent can be on any one of the four substitution sites, R1, R2, R3, and R4, and the other three sites must include a blocking substituent. If, on the other hand, there are two non-blocking substituents, then they must be on different carbon atoms, and they must be _trans_ to each other.

Preferably, the non-blocking substituent is either hydrogen or methyl, but most preferably, hydrogen. Preferably, the blocking substituent is either a phenyl group or a tertiary butyl group, but most preferably a phenyl group.

The substituents on the Y3 and Y6 sites affect the conformation of the ligand and thus have an influence on enantioselectivity in the epoxidation. Preferably, Y3 and Y6 are hydrogen, methyl, alkyl, or aryl. More preferably, they are hydrogen or methyl. Most preferably, they are hydrogen.

The Y1, Y2, Y4, and Y5 sites are seen to be less critical. Preferably, these sites are occupied by hydrogen, although these sites may also be occupied by substituents independently selected from the group consisting of hydrogen, halides, alkyls, aryls, alkoxy groups, nitro groups.

FIGURE 2 shows the structure of the most preferred embodiment of this first aspect of the present invention catalyst. As can be seen, the most preferred substituent at X1 and X3 is a t-butyl group. Also, it is most preferred for the R1 and R4 sites to have the same blocking group, namely a phenyl group. In addition, it is most preferred to have the R2 and R3 sites occupied by a hydrogen. Finally, it is most preferred that the X2, X4, Y1, Y2, Y3, Y4, Y5, and Y6 sites are also all occupied by a hydrogen.

While not wishing to be bound by any particular theory, the following mechanism has been proposed to explain the remarkable enantioselectivity of the first aspect of the present invention catalyst. Referring to FIGURE 4, which is a 3-dimensional view of the R,R enantiomer of the most preferred catalyst in its proposed oxo-intermediate state, it is seen that, with important exceptions, the salen ligand assumes a generally planar conformation with the oxygen atom 11 being complexed with the Manganese ion 13 and aligned on an axis generally perpendicular to this plane. The exceptions are the tert-butyl blocking groups attached at the X1 and X3 sites 15 and 17 respectively, and the phenyl blocking groups attached at the R1 and R3 sites 21 and 23, respectively. Although hard to depict in two dimensions, the phenyl blocking group 23 at R4 is behind the phenyl blocking group 21 at R1, while the R4 phenyl blocking group 23 is substantially above the plane of the catalyst and the R1 phenyl blocking group 21 is substantially below the plane of the catalyst.

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FIGURES 5A-5C show the different transition orientations possible for a cis-disubstituted olefin, namely cis-methylstyrene, which are possible during epoxidation of the double bond.

FIGURE 5A shows the favored orientation, i.e. the orientation with the least steric hindrance between the olefin and the blocking groups of the catalyst. This orientation results when the double bond approaches the oxygen atom from the front (as shown). This orientation results in the formation of the 1R,2S enantiomer of the cis-ß-methylstyreneoxide.

FIGURE 5B shows an orientation wherein methylstyrene has been rotated 180 degrees thus bringing the phenyl group of the styrene closer to the t-butyl groups 15 and 17 at the X1 and X3 positions. It is expected that steric hindrance between the phenyl group of the styrene 25 and the t-butyl groups 15 and 17 would disfavor this orientation.

FIGURE 5C shows an orientation resulting from the double bond approaching the oxygen atom from behind (as shown). This orientation results in the formation of the 1S,2R enantiomer of the cis-ß-methylstyrene oxide. In this orientation the phenyl group of the styrene 25 is closer to the phenyl group 23 on the R4 site. Steric hindrance between these two phenyl groups would thus disfavor this approach from behind the oxygen atom, and thus disfavor synthesis of the 1S,2R enantiomer.

In contrast, the orientation shown in FIGURE 5A results from an approach from the front, i.e. the side where the R1 phenyl group 21 is below the plane of the catalyst, and thus not in the way. For this reason, the approach depicted in FIGURE 5A is sterically favored, and thus synthesis of the 1R,2S enantiomer is favored.

It should be borne in mind that, although the above-described mechanism accurately predicts the high degree of enantioselectivity observed in the catalysts of the present invention, the mechanism is at present only a theory. As such, the proposed mechanism should in no way limit the scope of the present invention as defined by the appended claims.

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It is noted that synthesis of the 1S,2R enantiomer of the cis-ß-methylstyrene oxide is favored by using the S,S enantiomer of the catalyst.

It is also noted that this most preferred catalyst has C_2 symmetry, i.e. it is identical when rotated 180 degrees. Consequently,

5   whether the oxygen atom is aligned on the top of the catalyst as shown, or the bottom of the catalyst, the result is exactly the same.

In alternative embodiments, the catalyst has only approximate C_2 symmetry. In particular, as per the rules described above, the groups are positioned on R1-R4 so that when rotated 180°, the blocking groups are in the

10   same place and the non-blocking groups are in the same place. Consequently, the enantioselectivity of the catalyst is maintained because the oxygen can be complexed to either side of the catalyst while achieving roughly the same steric hindrances which favor the approach of the prochiral olefin from one side.

15   In other alternative embodiments, the catalyst has only one non-blocking group. As a result, there is a favored approach only when the oxygen is aligned on one side of the catalyst. Thus, the enantioselectivity of the catalyst is maintained.

The Second Aspect of the Invention

20   In accordance with the second aspect of the present invention, the chiral catalyst is made with a binaphthyl diamine and has the following general structure (see also FIGURE 3):
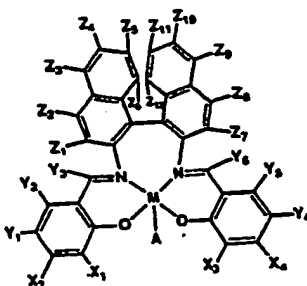
- 20 -

In this binaphthyl embodiment, the transition metal ion M and the anion A are preferably selected from the same group as that discussed above with FIGURE 1. Also as above, it is required that at least one of X1 and X2 together with at least one of X3 and X4 are occupied by a group
5   selected group of blocking substituents consisting of secondary or tertiary alkyl groups, aryl groups, silyl groups, and alkyl groups bearing heteroatom substituents such as alkoxy or halide. Preferably, it is the X1 and X3 sites which bear one of these substituents. More preferably, X1 and X3 bear the same substituent, which substituent is most preferably a tertiary alkyl group,
10   such as tertiary butyl.

The substituents on the Y3 and Y6 sites affect the conformation of the ligand and thus have an influence on enantioselectivity in the epoxidation. Preferably, Y3 and Y6 are hydrogen, methyl, alkyl, or aryl. More preferably, they are hydrogen or methyl. Most preferably, they are
15   hydrogen.

The substituents Z1 and Z2 affect the differentiation between the faces of the proposed metal oxo and thus have an influence on enantioselectivity in the epoxidation. Preferably, Z1 and Z2 are hydrogen, ethyl, alkyl, silyl, or aryl. More preferably, they are alkyl or aryl groups.
20   The Y1, Y2, Y4, and Y5 sites on the catalyst of this second aspect are also seen to be less critical. As above, these sites are preferably occupied by hydrogen, although these sites may also be occupied by substituents independently selected from the group consisting of hydrogen, halides, alkyls, aryls, alkoxy groups, nitro groups.
25   As can be visualized, this binaphthyl alternative embodiment effects the same enantioselectivity as that of the preferred catalysts shown in the other figures. In particular, the configuration of the binaphthyl ligand provides for one of the naphthyl groups to be above the plane of the catalyst and the other naphthyl group to be below the plane of the catalyst, thereby
30   favoring approach to the oxygen atom from one side.

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The Third Aspect of the Invention

FIGURE 6 shows the structure f the third aspect of the present invention. In accordance with this aspect, the chiral catalyst has the following structure:

5
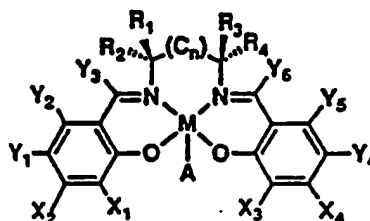
As with the first and second aspects, M is a transition metal ion selected from the group mentioned above, with Mn being the most preferred.

Likewise, A is an anion selected from the group mentioned above, with Cl being most preferred.

10   Also, n can be 0, 1, or 2, but 0 is the most preferred.

As with the first and second aspects, there is a blocking substituent on either X1 or X2 or on both. This blocking substituent is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms. There is also a blocking substituent selected from

15   the same group on either X3 or X4 or on both. Preferably, the blocking substituents are at X1 and X3. More preferably they are the same group, and most preferably the blocking substituents are tert-butyl.

As a point of difference with the first aspect, the third aspect requires a blocking substituent located at the following positions: at least one

20   of Y1 and Y2, and at least one of Y4 and Y5. These blocking substituents are selected from the group as those for X1-X4, namely the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms. The importance of these "side" blocking substituents will be discussed below.

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In this third aspect, substituents Y3 and Y6 are independently selected from the group consisting of hydrogen and primary alkyl groups. Preferably, Y3 and Y6 are hydrogen.

Also in this third aspect, at least one of R1, R2, R3 and R4 is hydrogen. Where R1 is hydrogen, R3 is a primary alkyl. Where R2 is hydrogen, R4 is a primary alkyl. Where R3 is hydrogen, R1 is a primary alkyl. Finally, where R4 is hydrogen, R2 is a primary alkyl. Preferably, R1 and R4 are both hydrogen and R2 and R3 are primary alkyls. Most preferably, R2 and R3 are methyl groups.

As can be seen, the catalyst of this third aspect is similar to the catalyst of the first aspect with the exception that the third aspect requires blocking substituents at the side positions of the catalyst, i.e. on the Y1 and/or Y2, and Y4 and/or Y5 sites. Also, either one or two of R1, R2, R3 and R4 is required to be an hydrogen, with the remaining substituents at the R sites required to be primary alkyls in the defined arrangement. The importance of this configuration and the proposed mechanism for the second catalyst are discussed below in connection with FIGURE 10.

The Fourth Aspect of the Invention

FIGURE 7 shows the structure of a catalyst of the fourth aspect of the invention. This catalyst has the following structure:
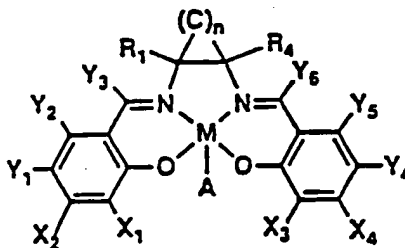
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In this embodiment, the transition metal, M, and the anion, A, are selected from the same groups as above, with the same preferences.

Likewise, the substituents at X1, X2, X3, X4, Y1, Y2, Y4, and Y5 are selected from the same groups as in the second catalyst described

5   above with the same preferences. In other words, this embodiment requires blocking substituents at the "bottom" and "sides" as does the second catalyst. Most preferably, X1, X3, Y1, and Y4 are all t-butyl.

The requirements and preferences for Y3 and Y6 are the same as with the third aspect. Preferably, Y3 and Y6 are hydrogen.

10   As can be seen, this catalyst of the fourth aspect of the invention includes a ring attached to the two nitrogen atoms, which ring is n+2 carbons long. In this catalyst, n can be 3, 4, 5 or 6. The carbons in the "C_n" portion can have substituents selected from hydrogen, alkyl, aryl, and hetero atoms. Preferably, the substituents on the carbons in the "C_n" portion are hydrogen.

15   In this fourth aspect, R1 and R4 are configured so as to be _trans_ to each other. Also, R1 and R4 are selected from the group consisting of primary alkyls and hydrogen. Preferably, R1 and R4 are the same. Most preferably, both R1 and R4 are hydrogen. Most preferably, this catalyst is used to epoxidize cis-cinnamate derivatives (see below).

20   Conceptually, the carbons in the ring which are adjacent the carbons which in turn are adjacent the nitrogen atoms are attached to what were shown as the R2 and R3 sites in the third aspect (FIGURE 6). Thus, this fourth aspect is, in some respects, a subset of the third aspect with the two ends of the n carbon chain (a primary alkyl) being attached to the R2 and R3

25   sites.

One distinction between the third and fourth aspects is that the catalyst of the fourth aspect has R1 and R4 which can be either hydrogen or a primary alkyl.

FIGURE 8 shows a preferred embodiment of this fourth aspect

30   of the invention. As can be seen in this embodiment, the ring is six-membered, that is, n=4. Also, R1 and R4, which are _trans_ to each other, are

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hydrogen. X1, X3, Y1, and Y4 are all t-butyl. All other substituents are
hydrogen.

FIGURES 9 and 10 illustrate the distinction between the
mechanism proposed for the first and second aspects of the invention and the
5   proposed mechanism for the third and fourth aspects.

FIGURE 9, representing the first and second aspects, shows the
proposed favored approach of the prochiral olefin. Approach c is believed to
be disfavored by the bulky t-butyl groups. Approach d is similarly
unfavorable, due to the steric bulk of the phenyl groups on the catalyst.
10   Approaches a and b are differentiated by the dissymmetry of the catalyst. As
shown in the depicted embodiment, because the phenyl to the left is below the
page and the phenyl to the right is above the page, it is predicted that approach
b will be less favorable due to steric interactions between the olefin and the
phenyl group. In the context of the more favored approach from the left
15   (approach a), it is predicted that the more favorable approach of the olefin to
the oxo group is such that the larger substituent on the olefin is oriented away
from the t-butyl groups on the catalyst.

FIGURE 10, representing the third and fourth aspects of the
invention, shows the proposed favored approach of the olefin when the catalyst
20   has side blocking groups. It is believed that, because of the side t-butyl
groups at Y1 and Y4, the approaches a from the left and b from the right are
disfavored. Likewise, because of the bottom blocking groups at X1 and X3,
the approach c from the bottom is also disfavored. Thus, approach d from the
top is favored. In addition, because of the chirality of the catalyst, the
25   orientation of the prochiral olefin is also influenced. As shown in this
depicted embodiment, because of greater steric hindrance on the right, the
olefin is predicted to orient itself with the larger group on the left.

Because approach d is theorized to be the favored approach, the
groups at R1 and R4 are limited to hydrogen and primary alkyls. In other
30   words, it is believed that larger groups would block the approach d.

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It should be noted that, although the above discussion is consistent with the observed results, the proposed mechanism for all four aspects of the invention is only theorized at this point. Consequently, the explanation is not to be viewed as limiting the scope of the invention as defined in the appended claims.

The preferred route to prepare the chiral catalysts of the present invention is a condensation reaction with the substituted salicylaldehyde and the substituted diamine. In general, quantities of these compounds are reacted in a 2 to 1 molar ratio in absolute ethanol. The solutions are refluxed typically for 1 hour, and the salen ligand is either precipitated in analytically pure form by addition of water, or the metal complex is generated directly by addition of the metal as its acetate, halide, or triflate salt.

The following procedure is general for the preparation of:
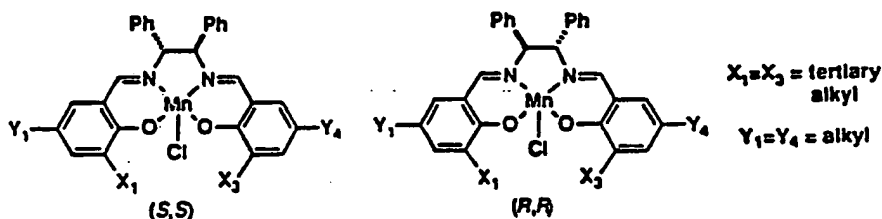
The salen ligand is redissolved in hot absolute ethanol to give a 0.1 M solution. Solid Mn(OAc)$_2$•4H$_2$O (2.0 equivalents) is added in one portion and the solution is refluxed for 1 h. Approximately 3 equivalents of solid LiCl are then added and the mixture is heated to reflux for an additional 0.5 h. Cooling the mixture to 0°C affords the Mn(III) complex 1 as dark brown crystals which are washed thoroughly with H$_2$O and isolated by filtration in ≈75% yield. An additional crop of material can be obtained by dropwise addition of H$_2$O to the mother liquor. Combined yields of catalyst are 89-96%

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for this step, and 81-93% overall from the optically pure 1,2-diphenylethylene diamine. Acceptable C, H, N, Cl, and Mn analyses of each of the catalysts have been obtained (±0.4%), although these vary according to the extent of water and ethanol incorporation in the powdery product. Enantioselectivities

5   in the epoxidation reactions did not vary among different batches of a given catalyst, indicating that the solvent content of the catalysts does not influence its effectiveness.

Another example of the method of preparing the catalyst is described as follows: Most preferably, the starting diamine is R,R- or S,S-

10   1,2-diamino-1,2-diphenylethane and the starting salicylaldehyde is 3-tert-butyl-salicylaldehyde.

A solution of 2.0 mmol of 3-tert-butylsalicylaldehyde in 3 ml of absolute ethanol is added dropwise to a solution of 1.0 mmol of (R,R)-1,2-diamino-1,2-diphenylethane in 5 ml of ethanol. The reaction mixture is heated

15   to reflux for 1 h and then 1.0 mmol of $Mn(OAc)_2•4H_2O$ is added in one portion to the hot (60°C) solution. The color of the solution immediately turns from yellow to brown upon addition. It is refluxed for an additional 30 min and then cooled to room temperature. A solution of 10% NaCl (5ml) is then added dropwise and the mixture stirred for 0.5h. The solvents are then

20   removed in vacuo and the residue is triturated with 50 ml of CH_2Cl_2 and 50 ml of H_2O. The organic layer is separated and the brown solution was washed with saturated NaCl. Separation of the organic phase and removal of solvent resulted in a crude material which was recrystallized from C_6H_6/C_6H_{14} to give 0.938 mmol of the (R,R)-catalyst shown above (93.8%).

25   In accordance with the epoxidation method aspect of the invention, the prochiral olefin, an oxygen atom source, and the chiral catalyst are reacted under such conditions and for such time as is needed to epoxidize said olefin.

The prochiral olefin can be selected from mono-substituted, 1,1-

30   disubstituted, cis-1,2-disubstituted, trans-1,2-disubstituted, trisubstituted, and

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tetrasubstituted. Of these, the monosubstituted and cis-1,2-disubstituted have shown the highest ee values.

Preferably, the prochiral olefin to be epoxidized is selected from the group consisting of cis-disubstituted olefins, including cyclic olefins, bearing a sterically demanding substituent on one end and a smaller substituent on the other end. More preferably, the prochiral olefin is a cis disubstituted olefin with a primary substituent on one side of the double bond and a secondary, tertiary, or aryl substituent on the other side.

The prochiral olefin can also be selected from the group consisting of enamines, enols, and alpha, beta-unsaturated carbonyls. More preferably, the prochiral olefin is selected from the group consisting of cis-ß-methyl-styrene, dihydronaphthalene, 2-cyclohexenyl-1,1-dioxolane, propylene, styrene and 2,2-dimethylchromene. Most preferably, the prochiral olefin is cis-ß-methylstyrene.

The oxygen atom source used in the epoxidation reaction should be an oxidant which is relatively unreactive toward olefins under mild conditions. Preferably, the oxygen atom source is selected from the group consisting of NaOCl, iodosylmesitylene, NaIO$_4$, NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, and hexacyanoferrate ion. More preferably, the oxygen atom source is selected from the group consisting of NaOCl and iodosomesitylene. For economic reasons, the most preferred oxygen atom source is NaOCl.

A preferred method uses NaOCl as the oxygen atom source. For convenience this method will be designated METHOD A. The details of METHOD A are as follows:

A solution of 0.05 M Na$_2$B$_4$O$_7$ 10H$_2$O (1.0ml) is added to a 2.5 ml solution of undiluted commercial household bleach (Chlorox). The pH of the resulting buffered solution is approximately 9.5, and it is adjusted to a pH of about 10.5 by addition of a few drops of 1 M NaOH solution. To this solution is added a solution of 0.02 mmol of the preferred catalyst and 1.0 mmol of cis B methylstyrene in 2.0 ml of CH$_2$Cl$_2$. The two-phase mixture is

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stirred at room temperature and the reaction progress is monitored by capillary gas chromatography. After approximately 3 hours, 10 ml of CH_2Cl_2 is added to the mixture and the brown organic phase is separated, washed twice with 10 ml H_2O and once with 10 ml saturated NaCl solution, and then dried for 15 minutes over anhydrous Na_2SO_4. The solution is filtered and solvent is removed under vacuum. The residue is purified by flash chromatography on silica gel using a 20:80 mixture of CH_2Cl_2:hexane as the eluting solvent. Pure epoxide is isolated as a colorless liquid in 70% yield (0.70 mmol) by combination of the product-containing fractions and removal of solvent under vacuum. The optical purity of this material is determined to be 85% ee by the method described below.

In a slightly less preferred embodiment, iodosylmesitylene is used as the oxygen atom source. For convenience, this method is designated as METHOD B and has the following preferred details: A solution of 1.0 mmol of olefin, 8 ml CH_2Cl_2 and 0.04 mmol of the catalyst are stirred at room temperature as solid iodosomesitylene is added in 0.3 mmol portions at 15-30 minute intervals. Disappearance of starting olefin is complete after addition of 6 portions (1.8 mmol) of total iodosylmesitylene. Solvent is removed in vacuo, the residue is extracted with hexane, and the mixture was filtered through Celite to remove catalyst and other solids. Pure epoxide was obtained by flash chromatography (10g SiO_2, CH_2Cl_2/hexane 20:80 eluent). Enantiomeric excesses are determined by 1H NMR using Eu(hfc)$_3$ as a chiral shift reagent, or in the case of stilbene oxide by direct separation by HPLC on a commercial (Regis) covalently-bound leucine Pirkle column. Absolute configurations were assigned by comparison of αD with accepted literature values.

An alternative method also uses a pyridine-N-oxide derivative as a coordinating ligand, in addition to NaOCl as the oxygen source. More preferably, 4-phenylpyridine-N-oxide or 4-t-butylpyridine-N-oxide is used. Even more preferably, 4-phenylpyridine-N-oxide is used.

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The trans-epoxide is a significant (about 25%) by-product of the epoxidation reaction. Preferably, the mixture of diastereomeric products is enriched in the desired cis- form by flash chromatography. Even more preferably, for large scale batches, no chromatography is not performed.

The next steps are shown in Scheme 2.

Scheme 2
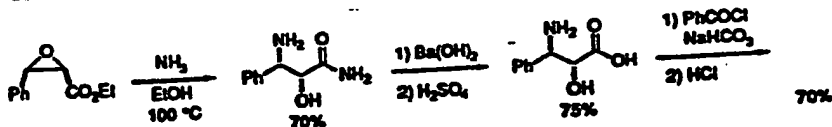
The epoxide mixture is reacted with ammonia in ethanol, which results in regioselective ring-opening to the desired 3-phenyl-isoserine amide derivative. Preferably, very little regioisomer is detected in the crude amide mixture by ^{1}H NMR. Next, diastereomerically pure 3-phenyl-isoserinamide is isolated by recrystallization of the crude product mixture. For convenience this method will be designated METHOD C. The details of METHOD C are as follows:

A solution of 0.05 M $Na_2B_4O_7$ • $10H_2O$ (1.0ml) or other suitable buffer such as phosphate is added to a 2.5 ml solution of undiluted commercial household bleach (Chlorox®). The pH of the resulting buffered solution is approximately 9.5, and it is adjusted to a pH of about 10.5-11.5 by addition of a few drops of 1 M NaOH solution and cooled in an ice bath to about 0-4° C. A separate solution of 10 mmol of alkene and 2.0 mmol (or 20 mol%) of a pyridine-N-oxide derivative are dissolved in 10 ml of CH_2Cl_2. Next, 0.05-0.6 mmol (0.5-6 mol%) of catalyst 1 or 2 were added to the alkene solution and
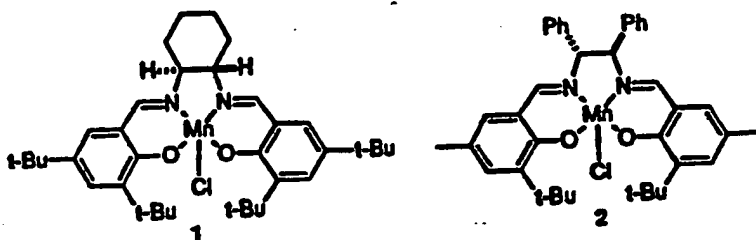
cooled separately in an ice bath. When the two solutions were at 0-4° C, they were combined, and the two-phase mixture was stirred. The reaction progress was monitored by capillary gas chromatography. After about one to five hours, 200 ml of hexane was added to the mixture and the organic phase was

5   separated, washed twice with 100 ml H_2O and once with 100 ml saturated NaCl solution, and then dried for 15 minutes over anhydrous Na_2SO_4. The solution is filtered and solvent is removed under vacuum. The residue is purified by chromatography, distillation or crystallization. Pure epoxides were isolated, and the optical purity of the materials were determined as described

10   in more detail below.

Method of Chromene Epoxidation

As noted above, the present invention is a method of using a chiral catalyst to epoxidize a chromene derivative, thus producing an epoxychroman. The structure of the chromene derivative is as follows:
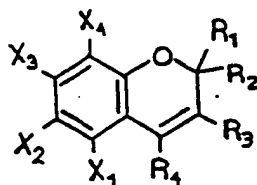
15

wherein R1, R2, R3, R4, X1, X2, X3, and X4 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms, and wherein no more than one of R1 and R2 are hydrogen.

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It has been found that when both R1 and R2 are hydrogen, i.e. when the chromene is not substituted at the R1 and R2 locations, the epoxide is not formed (see Example 24 below).

Preferably, R1 and R2 are the same group. In this situation, the
5 chromene derivative is prochiral.

Also, the chromene derivative preferably includes an alkyl group at both R1 and R2. More preferably, the chromene derivative includes a methyl group at R1 and R2. Most preferably, the chromene derivative is 6-cyano-2,2-dimethylchromene, namely the precursor for making cromakalim.
10 As mentioned above, this most preferred chromene derivative can be epoxid-ized with a remarkably high degree of enantioselectivity to the epoxychroman useful in producing enantiomerically pure cromakalim (see Example 17 below).

As noted above, this embodiment of the present invention has
15 been found to produce remarkable enantioselectivity in the epoxidation of chromene derivatives. In addition, the catalysts of the present invention have been found to provide remarkably high yields (See Examples 17-23, and 25 below). The catalyst of the fourth aspect (FIG. 8) above is the most preferred catalyst used in the present method. Experiments have shown that when a
20 racemic mixture of the chiral catalysts are used in the reaction that relatively high yields of a racemic mixture of the epoxychromans are achieved. Consequently, in accordance with a less preferred embodiment of the invention, when a racemic mixture of the epoxychromans is desirable or acceptable, a racemic mixture of the chiral catalyst is used with the chromene
25 derivatives. Nevertheless, because enantiomerically pure epoxychromans are typically highly desirable, particularly as synthetic precursors, enantiomerically pure chiral catalysts are clearly preferred.

In accordance with the epoxychroman synthetic method of the present invention, the chromene derivative, an oxygen atom source, and the
30 chiral catalyst are reacted under such conditions and for such time as is needed

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to epoxidize said chromene derivative. Alternatively, a pyridine-N-oxide derivative is added to the reaction mixture.

5   The oxygen atom source used in the epoxidation reaction should be an oxidant which is relatively unreactive toward olefins under mild conditions. Preferably, the oxygen atom source is selected from the group consisting of NaOCl, iodosylmesitylene, $NaIO_4$, NBu_4IO_4, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H_2O_2, peroxybenzoic acid derivatives, and hexacyanoferrate ion. More preferably, the oxygen atom source is selected from the group consisting of NaOCl and iodosylmesitylene.

10   For economic reasons, the most preferred oxygen atom source is NaOCl.

In the most preferred method for chromene epoxidation, NaOCl is the oxygen atom source, as described above for METHOD A. In a slightly less preferred embodiment, iodosylmesitylene is used as the oxygen atom source, as described above for METHOD B. Alternatively, a pyridine-N-

15   oxide derivative and NaOCl are used, as described in METHOD C.

Method of Epoxidation of cis-Cinnamate Derivatives and
Preparation of Taxol Intermediates and Analogs

As a first step in the synthesis of the C-13 side chain of taxol, commercially available ethyl phenylpropiolate is partially hydrogenated to cis-

20   ethyl cinnamate over commercial Lindlar's catalyst (Scheme 1 below). Because the reaction was observed to be more enantioselective, ethyl phenylpropiolate is preferred over methyl phenylpropiolate as a starting material.


Scheme 1
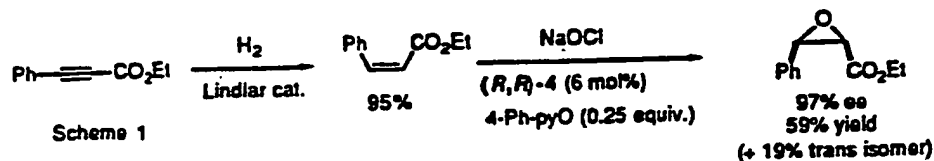
25   The cis-ethyl cinnamate thus obtained has been observed to contain small amounts (about 5%) of overreduced material and starting alkyne.

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However, these impurities do not appear to interfere with subsequent steps and are easily removed later in the synthetic sequence.

Next, cis-ethyl cinnamate is epoxidized with commercial bleach in the presence of one of the chiral catalysts discussed above as the first, second third and fourth embodiments of the invention. Most preferably, the fourth embodiment of the invention (the (R,R) 5 catalyst of Figure 8) is employed and is shown below:
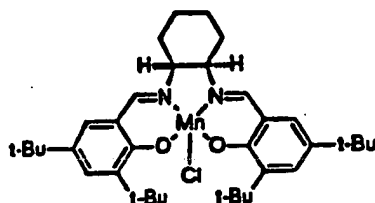

In the presence of this enantioselective catalyst, the cis-ethyl cinnamate was observed to epoxidize to the (R,R)-(+) enantiomer of the cis-epoxide.

Preferably, 4-phenylpyridine-N-oxide is added to the epoxidation mixture. This coordinating ligand appears to markedly enhance reaction completion and enantioselectivity. With the use of 4-phenylpyridine-N-oxide, the (R,R)-(+)- enantiomer of cis-ethyl cinnamate epoxide was in excess of 96-97%. Either a less preferred pyridine-N-oxide derivative, or 4-t-butylpyridine-N-oxide may be used, but 4-phenylpyridine-N-oxide is preferred.

The trans-epoxide is a significant (about 25%) by-product of the epoxidation reaction. Preferably, the mixture of diastereomeric products is enriched in the desired cis- form by flash chromatography. Even more preferably, for large scale batches, no chromatography is not performed.

The next steps are shown in Scheme 2 below.

Scheme 2
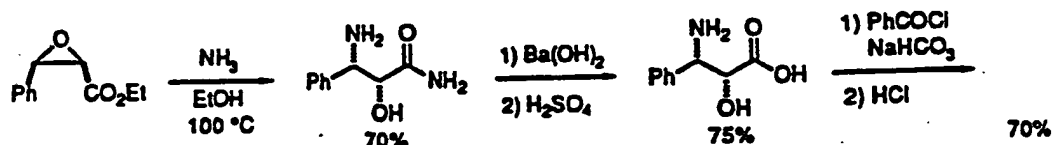
- 34 -

The epoxide mixture is reacted with ammonia in ethanol, which results in regioselective ring-opening to the desired 3-phenyl-isoserine amide derivative. Very little regioisomer has been detected in the crude amide mixture by ^1H NMR. Next, diastereomerically pure 3-phenyl-isoserinamide was isolated by
5   recrystallization of the crude product mixture.

The 3-phenyl-isoserinamide is hydrolyzed to remove the amide group. Preferably, the hydrolysis is effected without epimerization. Even more preferably, the hydrolysis is effected by using Ba(OH)$_2$ in water.

Next, the hydrolyzing salt is acidified and precipitated.
10   Preferably, if Ba(OH)$_2$ salt is used for hydrolysis, it is next precipitated out of the solution by addition of sulfuric acid.

Next, 3-phenyl-isoserine is obtained directly by crystallization of the product mixture. This enantiomerically enriched 3-phenyl-isoserine is used to prepare a wide variety of taxol analogs. Preferably, the taxol side chain
15   benzoyl derivative is prepared from 3-phenyl-isoserine.

The taxol side chain is prepared by adding to the 3-phenyl-isoserine formed above benzoyl chloride and sodium bicarbonate in an acid two-phase reaction. Subsequently, the benzoic acid by-product is extractively removed by stirring the solid product mixture with ether and ethanol. Finally,
20   pure N-benzoyl-3-phenyl-isoserine is collected by filtration. The material thus obtained was determined by polarimetry to have an ee of more than 97% and to have the same absolute configuration as the side chain from natural taxol.

The N-benzoyl-3-phenyl-isoserine is reacted to produce N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine, which in turn is reacted with a
25   tertiary amine activating agent and 7-triethylsilyl baccatin III to form a C-2', C-7-protected taxol derivative. This derivative is treated with acid in ethanol to produce taxol.

While not wishing to be bound by this theory, it appears that 4-phenylpyridine-N-oxide effectively increases the success of the

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enantiomerically selection and complete epoxidation of cis-ethyl cinnamate to
the (R,R)-(+)-enantiomer of the cis-epoxide. In the absence of 4-phenyl-
pyridine-N-oxide, epoxidation is 10-15% less selective and is less complete,
even when 15-20 mol% more catalyst is used. Control experiments indicated

5   that the pyridine-N-oxide derivative did not act as the oxygen-atom source, but
rather as a coordinating ligand. It appears that coordination of pyridine-N-
oxide derivative to the mildly Lewis acidic Mn(III) and/or Mn(V) oxo
intermediate helps prevent the metallic center from remaining complexed with
by the carbonyl functionality on the substrate in a non-product coordination

10   mode. Thus, the pyridine-N-oxide derivative appears to prevent
decomposition reactions and improve catalyst stability with certain olefins,
although not all olefins.

The enantioselectivity of the reaction was also found to be quite
sensitive to the identity of the ester group on the starting material, with cis-

15   methyl cinnamate being epoxidized under similar conditions as cis-ethyl
cinnamate, but in only 87-89% enantiomeric excess.

The advantages of this synthetic method are that it begins with
commercially available ethyl phenylpropiolate and employs hydrogen gas,
household bleach, ammonia and barium salts as stoichiometric reagents.

20   Another advantage is the high optical and chemical purity of N-benzoyl-3-
phenyl-isoserine. As will become apparent in the examples 29 to 39 below,
the yields of each of the individual steps are acceptable for a commercially
feasible process, even though they have not yet been completely optimized.
The catalytic specificity, procedural simplicity, inexpensive reagents and

25.   avoidance of preparative chromatographic separations renders this synthetic
method a most practical route to enantiomerically pure 3-phenyl-isoserine
derivatives.

Method of Sulfide Oxidation

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As noted above, the present invention is a method of using a
chiral catalyst to enantioselectively oxidize a sulfide to a sulfoxide. The
method involves reacting a sulfide, an oxygen atom source, and a chiral
catalyst under the proper conditions to oxidize the sulfide. Preferably the

5   sulfide has the formula R1-S-R2 where R1 is any aromatic group and R2 is
any alkyl group. Preferably, the oxygen atom source is hydrogen peroxide or
iodosylbenzene and preferably, a cosolvent such as tetrahydrofuran, acetone,
or acetonitrile is used.

As described above, for enantioselective epoxidation by the

10 (salen)Mn catalysts, aqueous sodium hypochlorite was used as the
stoichiometric oxidant. However, the reaction between sulfides and sodium
hypochlorite was too rapid for this oxidant be useful for enantioselective
sulfide oxidation reactions. Iodosylbenzene was tried because iodosylarenes
react slowly with sulfides. It was found that iodosylbenzene did indeed serve

15 as an effective oxygen atom source. However, iodosylarenes are impracticable
as stoichiometric oxidants due to their instability in the solid state, their lack of
solubility, their relatively high cost and the high molecular weight of the
byproduct of oxygen transfer, an iodoarene.

Hydrogen peroxide was determined to be a good oxidant for

20 sulfide oxidation. Hydrogen peroxide gave higher yields of sulfoxide, minimal
overoxidation to sulfone and identical enantioselectivities to those observed
with iodosylbenzene. This suggests that both oxidants generate a common
Mn(V) oxo reactive intermediate.

To facilitate the reaction, a cosolvent was used. The cosolvent

25 minimized the catalase-decomposition of hydrogen peroxide by the catalysts
and a complete conversion of sulfide was accomplished with less than 6
equivalents of oxidant.

Generally, catalysts derived from 1,2-diaminocyclohexane and
1,2-diphenylethylene diamine were more selective than those prepared from

30 other synthetically less accessible diamines. FIGURES 19 and 20 show the
structures of the preferred catalysts. Specific catalysts based on these, were

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tested for asymmetric sulfide oxidation and Example 40 lists the results of the tests.

Catalytic Disproportionation of Hydrogen Peroxide

As mentioned above, the decomposition of hydrogen peroxide
5 into oxygen and water is a biologically important process. All of the catalysts described so far are useful in the catalytic disproportionation of hydrogen peroxide. However, for this particular reaction, the catalysts do not have to be chiral. Thus, any catalyst having the following formula will function in the decomposition reaction:
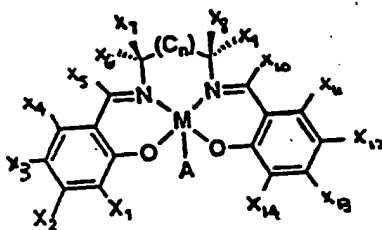
10 wherein M is a transition ion, A is an anion, n is either 0, 1, or 2 and X1 through X14 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls and alkyl groups bearing hetero atoms.

The catalysts of the present invention are stable, easy to synthesize, have a low molecular weight and a high catalytic activity. In fact
15 their catalytic activity is comparable to any synthetic catalase mimic developed to date. The preferred catalysts are the monometallic (salen)Mn complexes shown in FIGURES 22 and 23.

To carry out the disproportionation reaction, the catalyst is mixed with a solvent such as EtOH, acetone, CH_2Cl_2, or H_2O and then
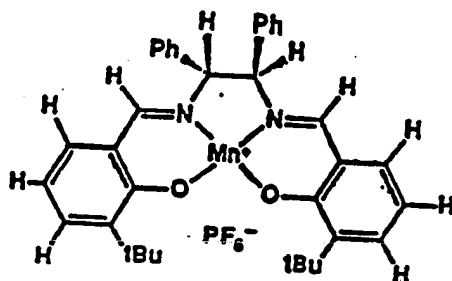20 hydrogen peroxide is added.

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EXAMPLES

The following examples are provided by way of explanation and illustration. As such, these examples are not to be viewed as limiting the scope of the invention as defined by the appended claims.

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Preparation of the Catalysts

Procedures for the Preparation of Chiral Salen Based Catalysts

Preparation of:

5   (R,R)-1,2-Diphenyl-1,2-bis(3-tert-butylsalicylideamino)ethane (2).

A solution of 360.5 mg (2.0 mmol) of 3-tert-butylsalicylaldehyde in 3 ml of EtOH was added dropwise to a solution of 212.3 mg (1.0 mmol) of (R,R)-1,2-diamino-1,2-diphenylethane in 5 ml of EtOH. The reaction mixture was heated to reflux for 1 h and water (5 ml)

10   was added. The oil that separated solidified upon standing. Recrystallization from MeOH/H$_2$O gave 485.8 mg (91%) of yellow powder, mp 73-74°C. ^{1}H NMR (CDCl$_3$) δ 1.42 (s, 18H, CH$_3$), 4.72 (s, 2H, CHN=C), 6.67-7.27 (m, 16H, ArH), 8.35 (s, 2H, CH=N), 13.79 (s, 2H, ArOH) ppm; 13C NMR (CDCl$_3$) δ 29.3, 34.8, 80.1, 117.8, 118.5, 127.5, 128.0, 128.3, 129.6, 130.1,

15   137.1, 139.5, 160.2, 166.8 ppm. Anal. Calcd. for C$_{36}$H$_{40}$N$_2$O$_2$. C, 81.17; H, 7.57; N, 5.26. Found: C, 81.17; H, 7.60; N, 5.25.

((R,R)-1,2-Diphenyl-1,2-bis(3-tert-butylsalicylideamino)ethane)-
manganese(II) Complex (3).

Under strictly air-free conditions, a solution of 64.0 mg (1.6

20   mmol) of NaOH in 2 ml of MeOH was added dropwise to a solution of 426. 1

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mg (0.8 mmol) of (2) in 5 ml of EtOH with stirring under an atmosphere of nitrogen. A solution of 196.1 mg (0.8 mmol) of $Mn(OAc)_2 \cdot 4H_2O$ in 3 ml of MeOH was added rapidly and the orange mixture was stirred for 24 hr. The solvent was removed in vacuo and the residue was stirred with 5 ml of benzene and filtered to remove NaOAc. The filtrate was concentrated to about 1 ml and 3 ml of hexane was added. The mixture was cooled to -30°C and the precipitate was collected by filtration to give 410.2 mg (87%) of orange powder. Anal. Calcd. for $C_{36}H_{38}MnN_2O_2-(CH_3OH)$ 0.5; C, 72.86; H, 6.70; N, 4.66. Found: C, 73.05; H, 6.76; N, 4.39.
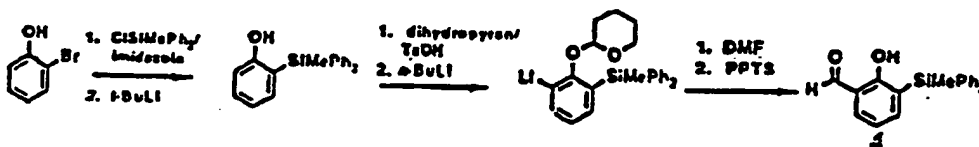

((R,R)-1,2-Diphenyl-1,2-bis(3-tert-butylsalicylideamino)ethane)-manganese(III) Hexafluorophosphate ((R,R)-1).

A solution of 165.5 mg (0.5 mmol) of ferrocenium hexafluoro-phosphate in 2 ml of CH_3CN was added dropwise to a solution of 292.8 mg (0.5 mmol) of (3) in 3 ml of CH_3CN under N_2. The reaction mixture was stirred for 30 min and the solvent was removed in vacuo. The residue was triturated with 5 ml of hexane and filtered. The solid was then washed with hexane until the filtrate was colorless and dried under vacuum to give 360.5 mg (93%) of (1) as a brown powder. IR (CH_2Cl_2) 2955, 1611, 1593, 1545, 1416, 1389, 1198, 841 cm^{-1}. Anal. Calcd. for $C_{36}H_{38}F_6MnN_2O_2P \cdot (H_2O)1.5 \cdot (CH_3CN)0.5$: C, 56.93; H, 5.30; N, 4.57. Found: C, 57.11; H, 5.50; N, 4.50.
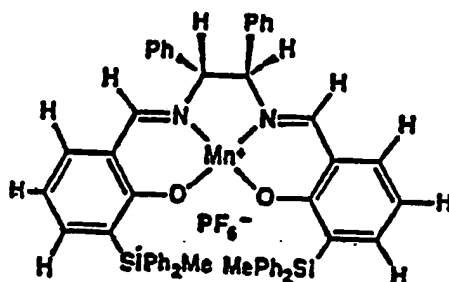
Preparation of:

The salicylaldehyde derivative _(4)_ was prepared by the following sequence using well-established procedures in each step:

(R,R)-1,2-Diphenyl-1,2-bis(3-diphenylmethylsilylsalicylideamino)ethane (5).

A solution of 348.3 mg (1.09 mmol) of _(4)_ and 116.0 mg (0.546 mmol) of (R,R)-1,2-diamino-1,2-diphenylethane in 5 ml of ethanol was heated to reflux for 0.5 h. A bright yellow oil separated from the solution and it solidified upon standing. The mixture was filtered and the yellow solid was washed with 2 x 5 ml ethanol. The isolated yield of product pure by ¹H NMR

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analysis was 416 mg (97%). ^{1}H NMR (CDCl$_3$) 80.95 (s, 3H), 4.68 (s, 2H), 6.72-7.55 (m, 36H, ArH), 8.37 (s, 2H), 13.34 (s, 2H) ppm.

((R,R)-1,2-Diphenyl-1,2-bis(3-diphenylmethylsilylsalicylideamino)ethane)-manganese(II) Complex (6).

5   Under strictly air-free conditions, a solution of 32.0 mg (0.48 mmol) of KOH in 2 ml of ethanol was added dropwise to a suspension of 195 mg (0.24 mmol) of (5) in 3 ml of ethanol with stirring. The heterogeneous mixture was stirred for 20 min, and a solution of 51.5 mg (0.24 mmol) of Mn(OAc)$_2$•4H$_2$O in 3 ml of MeOH was then added rapidly.

10 The yellow-orange mixture was stirred for 8 hr. at room temperature, then refluxed under N$_2$ for 4 hr. The solvent was removed in vacuo and the residue was washed with 5 ml of methanol, 5 ml of ethanol, and isolated by filtration. The yield of orange product was 188 mg (90%). This material was used in the next step without any further purification or analysis.

15 **((R,R)-1,2-Diphenyl-1,2-bis(3-diphenylmethylsilylsalicylideamino)ethane)-manganese(III) Hexafluorophosphate ((R,R)-1(7).**

      A solution of 72 mg (0.217 mmol) of ferrocenium hexafluoro-phosphate in 2 ml of CH$_3$CN was added dropwise to a solution of 188 mg (0.217 mml) of (6) in 3 ml of CH$_3$CN under N$_2$. The reaction mixture was

20 stirred for 30 min and the solvent was removed in vacuo. The solid residue was then washed with hexane until the filtrate was colorless. The brown powder was dried under vacuum to give 201.3 mg (92%) of (7). Anal. Calcd. for C$_{54}$H$_{46}$F$_6$MnN$_2$O$_2$PSi$_2$•(CH$_3$CN)1.5•(H$_2$O): C, 62.77; H, 4.85; N, 4.50. Found: C, 62.89; H, 4.47; N, 4.57.

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Preparation of:
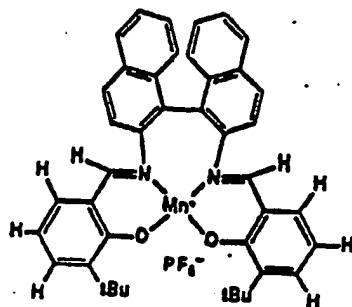
2,2'-Bis(3-tert-Butylsalicylideamino)-1,1'-Binaphthyl.

  A solution of 725 mg (4.0mmol) of 3-tert-butyl-salicylaldehyde

in 6 ml of EtOH was added dropwise to a solution of 569 mg (2.0 mmol) of

(+)-2,2'-diamino-1,1-binaphthyl in 5 ml of EtOH. The reaction mixture was

heated to reflux for 8 h and then volatile materials were removed under

vacuum. The residue was purified by flash chromatography on 80 g SiO2,

using 20% CH_2Cl_2 in hexane as eluent. The mobile yellow fraction was

collected and solvents were removed under vacuum to give 725 mg (1.20

mmol, 59% yield) of the diimine as a yellow powder.

**1,1'-Binaphthyl-2,2'-bis(3-tert-Butylsalicylideamino)-manganese(II)
Complex.**

  Under strictly air-free conditions, a solution of 2 mmol of KOH

in 2 ml of MeOH is added dropwise to a solution of 1 mmol of 2,2'-bis(3-tert-

butylsalicylideamino)-1,1'-binaphthyl in 5 ml of EtOH with stirring under an

atmosphere of nitrogen. A solution of 1 mmol of $Mn(OAc)_2 \bullet 4H_2O$ in 3 ml of

MeOH is added rapidly and the orange mixture is stirred for 24 hr. The

solvent is removed in vacuo and the residue was stirred with 5 ml of benzene

and filtered to remove KOAc. The filtrate is concentrated to dryness to afford

the Mn(II) complex as an orange powder.

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1,1'-Binaphthyl-2,2'-bis(3-tert-Butylsalicylideamino)-manganese(III) Hexafluorophosphate.

A solution of 165.5 mg (0.5 mmol) of ferrocenium hexafluoro-
phosphate in 2 ml of CH_3CN is added dropwise to a solution of 0.5 mmol of
5   1,1'-binaphthyl-2,2'-bis(3-tert-butylsalicylideamino)-manganese(II) complex in
3 ml of CH_3CN under N_2. The reaction mixture is stirred for 30 min and the
solvent is removed in vacuo. The residue is triturated with 5 ml of hexane
and filtered. The solid is then washed with hexane until the filtrate is colorless
and dried under vacuum to give the Mn(III) salt as a deep green powder.

10   Preparation of:
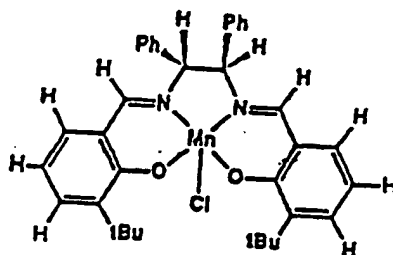
No precautions to exclude air or moisture were necessary in this
procedure. A solution of 360.5 mg (2.0 mmol) of 3-tert-butylsalicylaldehyde
in 3 ml of absolute ethanol was added dropwise to a solution of 212.3 mg
15   (1.0 mmol) of (R,R)-1,2-diamino-1,2-diphenylethane in 5 ml of ethanol. The
reaction mixture was heated to reflux for 1 h and then 245.1 mg (1.0 mmol) of
$Mn(OAc)_2 \cdot 4H_2O$ was added in one portion to the hot (60°C) solution. Upon
addition, the color of the solution immediately turned from yellow to brown.
It was refluxed for an additional 30 min and then cooled to room temperature.
20   A solution of 10% NaCl (5 ml) was then added dropwise and the mixture
stirred for 0.5 h. The solvent was then removed in vacuo and the residue was
triturated with 50 ml of CH_2Cl_2 and 50 ml of H_2O. The organic layer was

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separated and the brown solution was washed with saturated NaCl. Separation
of the organic phase and removal of solvent afforded crude material which was
recrystallized from C_6H_6/C_6H_{14} to give 591 mg (0.938 mmol) of the chloride
salt of (1) (94%). Anal. Calcd. for $C_{36}H_{33}ClMnN_2O_2 \cdot (H_2O)0.5$: C, 68.63; H,
6.24; N, 4.45. Found: C, 69.01; H, 6.26; N, 4.38.

Procedure for the preparation of the most preferred catalyst of the fourth aspect of the invention

(R,R)- and (S,S)-1,2,-bis(3,5-di-tert-butylsalicylide-amino)cyclohexane

(S,S)   (R,R)
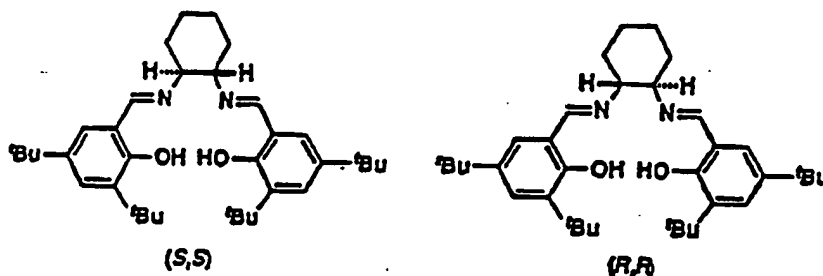
3,5-Di-t-butylsalicylaldehyde (2.0 equivalents) was added as a
solid to a 0.2 M solution of (R,R) or (S,S) 1,2- diaminocyclohexane (1.0
equivalent) in absolute ethanol. The mixture was heated to reflux for 1 hr.
and then H_2O was added dropwise to the cooled bright yellow solution. The
resulting yellow crystalline solid was collected by filtration and washed with a
small portion of 95% ethanol. The yield of analytically pure salen ligan
obtained in this manner was 90-97%.

Spectroscopic and analytical data for the salen ligand: ^1H NMR
(CDCl$_3$) δ 13.72 (s, 1H), 8.30 (S, 1H), 7.30 (d, J = 2.3 Hz, 1H), 6.98 (d, J
= 2.3 Hz, 1H), 3.32 (m, 1H), 2.0-1.8 (m, 2H), 1.8-1.65 (m, 1H), 1.45 (m,
1H), 1.41 (s, 9H), 1.24 (s, 9H). ^{13}C NMR (CDCl$_3$): δ 165.8, 158.0, 139.8,

136.3, 126.0, 117.8, 72.4, 34.9, 33.0, 31.4, 29.4, 24.3. Anal. Calcd for $C_{36}H_{54}N_2O_2$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.12; H, 9.97; N, 5.12.

(R,R)- and (S,S)-[1,2-bis(3,5-di-tert-butylsalicylide-amino)cyclohexane]-manganese(III) chloride.

5   The salen ligand immediately above is redissolved in hot absolute ethanol to give a 0.1 M solution. Solid $Mn(OAc)_2$•$4H_2O$ (2.5 equivalents) is added in one portion and the solution is refluxed for 1 hr. Approximately 5 equivalents of solid LiCl are then added and the mixture is heated to reflux for an additional 0.5 hr. Cooling the mixture to 0°C and

10   addition of a volume of water equal to the volume of the brown ethanolic solution to afford the Mn(III) complex as a dark brown powder which are washed thoroughly with H_2O, and isolated by filtration in 81-93% yield. Acceptable C, H, N, Cl, and Mn analyses of the catalyst have been obtained (±0.4%), but these vary according to the extent of water and ethanol

15   incorporation in the powdery product. Enantioselectivities in the epoxidation reactions are invariant with different batches of a given catalyst, indicating that the solvent content of the catalyst does not influence its effectiveness.

Analytical data for this catalyst: Anal. Calcd for $C_{36}H_{52}ClMnN_2O_2$•C_2H_5OH: C, 67.19; H, 8.31; Cl, 5.22; Mn, 8.09; N, 4.12:

20   Observed: C, 67.05; H, 8.34; Cl, 5.48; Mn, 8.31; N, 4.28.

Procedures for the Asymmetric Epoxidation of Chromene Derivatives

Method A (NaOCl as oxygen atom source):

A solution of 0.05 M $Na_2B_4O_7$•$10H_2O$ (1.0 ml) was added to a 2.5 ml solution of undiluted commercial household bleach (Clorox®). The pH of the

25   resulting buffered solution was approximately 9.5, and it was adjusted to a pH of 10.5 by addition of a few drops of 1 M NaOH solution. To this solution was added a solution of about 0.005 to 0.02 mmol of the catalyst and

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about 1.0 mmol of olefin in 2.0 ml of CH_2Cl_2. The two-phase mixture was
stirred at room temperature and the reaction progress was monitored by
capillary gas chromatography. Reactions were complete within approximately
1-5 hours. After the reaction was complete, 10 ml of CH_2Cl_2 was added to the
5   mixture and the brown organic phase was separated, washed twice with 10 ml
H_2O and once with 10 ml saturated NaCl solution, and then dried for 15 min
over anhydrous Na_2SO_4. The solution was filtered and solvent was removed
under vacuum. The residue was purified by standard procedures using flash
chromatography on 10g of silica gel using a mixture of CH_2Cl_2/hexane as the
10   eluting solvent. Pure epoxide was isolated by combination of the product-
containing fractions and removal of solvent under vacuum. Enantiomeric
excesses were determined by ^{1}H NMR using Eu(hfc)$_3$ as a chiral shift reagent,
or in the case of stilbene oxide by direct separation by HPLC on a commercial
(Regis) covalently-bound leucine Pirkle column. Absolute configurations were
15   assigned by comparison of [α]D with accepted literature values.

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Method B (iodosylmesitylene as oxygen atom source)

A solution of 1.0 mmol of olefin, 8 ml CH$_2$Cl$_2$ and 0.04-0.08 mmol of the catalyst was stirred at room temperature as solid iodosomesitylene was added in 0.3 mmol portions at 15-30 minute intervals.

5   Disappearance of starting olefin was complete after addition of 4 10 portions (1.2 to 3 equivalents) of total iodosylmesitylene. Solvent was removed in vacuo, the residue was extracted with hexane, and the mixture was filtered through Celite diatomaceous earth to remove catalyst and other solids. Pure epoxide was obtained by flash chromatography (10g SiO$_2$, CH$_2$Cl$_2$/hexane

10   eluent). The optical purity of this material was determined by the method described above.

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Asymmetric Epoxidation of Representative Olefins with the most preferred embodiment of the first aspect.

Examples 1-7

Entry	Olefin[a]	Catalyst	Yield[b](%)	ee(%)	Config-uration[c]	Method
1		(R,R)-1	50	59	1R,2S-( )	B
2		(R,R)-1d	75	57	R-(+)	A
3		(R,R)-1d	72	67	(+)e	B
4		(R,R)-1	52	93	(-)e	B
5		(R,R)-1	70	85	1R,2S-(-)	A
6		(R,R)-1[d]	72	78	1R,2S-(+)	B
7		(R,R)-1	36	30	R-(+)	B

[a] Reactions were run at 25°C unless otherwise noted.
[b] Isolated yields based on olefin.
[c] The sign corresponds to that of $[\alpha]D$.
[d] Reaction run at 5°C.
[e] Absolute configuration not known.

The table above shows that the highest enantiomeric excess (ee) values were observed with Examples 4, 5, and 6, i.e. cis disubstituted olefins. In contrast, Example 7, a 1,1 disubstituted olefin, had the lowest ee values. Example 1, a trans disubstituted olefin, and Examples 2 and 3, monosubstituted olefins, had intermediate ee values.

Asymmetric Epoxidation of Representative Olefins
with Catalysts from the first and fourth aspects of the invention.

Examples 8-16

       The following Examples 8-16 were run the same as Examples 1-

5   7, except that different catalysts were used. The key to the catalyst numbering

system is found in FIGURE 11. As can be seen, Example 8 was made

according to the most preferred embodiment of the first aspect.

Examples 9-16 were made according to the fourth aspect, with the catalyst

used in Examples 12-16 being the most preferred embodiment of the fourth

10   aspect. It is also noted that all of Examples 8-16 were run with method B

described above.

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TABLE II

Entry	Olefin[a]	Catalyst	Yield[b](%)	ee[c] (%)	Configuration[d]
8	Ph⌣Ph	(R,R)-1	70	85	1R,2S-(-)
9		(S,S)-2	75	49	1S,2R-(+)
10		(S,S)-3		80	1S,2R-(+)
11		(S,S)-4		55	1S,2R-(+)
12		(S,S)-5	82	92	1S,2R-(+)
13		(S,S)-5	74	94	
14		(S,S)-5	87	97	n.d.
15		(S,S)-5	53	94	R,R-(+)
16	Ph⌣CO₂Me	(S,S)-5	74	75	S,S-(-)

[a]Reactions were run at 0°C. [b]Isolated yields based on olefin. [c]Determined by ¹H NMR analysis in the presence of Eu(hfc)₃ and by capillary GC using a commercial shiral column (J & W Scientific Cyclodex-B column, 30 m x 0.25 mm I.D., 0.25 μm film). [d]All reactions were run in duplicate with both enantiomers of each catalyst. Reactions carried out with (R,R)-5 afforded epoxides with absolute configurations opposite to those in the table and with the same ee's (± 2%). The sign corresponds to that of [α]D.

---

[a]Reactions were run at 0°C. [b]Isolated yields based on olefin. [c]Determined by ¹H NMR analysis in the presence of Eu(hfc)₃ and by capillary GC using a commercial shiral column (J & W Scientific Cyclodex-B column, 30 m x 0.25 mm I.D., 0.25 μm film). [d]All reactions were run in duplicate with both enantiomers of each catalyst. Reactions carried out with (R,R)-5 afforded epoxides with absolute configurations opposite to those in the table and with the same ee's (± 2%). The sign corresponds to that of [α]D.

As shown in Examples 12-15, the most preferred catalyst of the fourth embodiment catalyzes the epoxidation of cis-disubstituted olefins with excellent enantioselectivity.
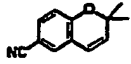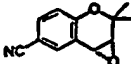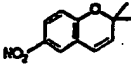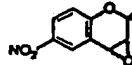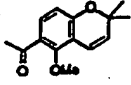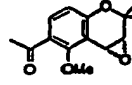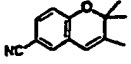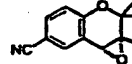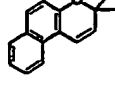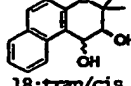
Examples 17-24 Epoxidation of Chromene Derivatives

The following Examples 17-24 were carried out to show the effectiveness of the present method to enantioselectively epoxidize various chromene derivatives. The catalyst used in these examples is the R,R enantiomer shown in Figure 8. The method described above as Method A was used for these examples:

The results are shown in Table III. It is noted that the unsubstituted chromene in Example 24 did not produce an epoxychroman.

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TABLE III

Example No.	Olefin	Major Product(s)	ee (%)[b]	Isolated Yield (%)[c]	Absolute Configuration
17	NC—	NC—	97	96	(3R,4R)-(+)[a]
18	NO₂—	NO₂—	94	76	(3R,4R)-(+)[a]
19			98	87	(3R,4R)-(+)[a]
20			90[d]	75	(3R,4R)-(+)[e]
21			97[f]	51	(3R,4R)-(+)[a]
22	NC—	NC—	>98	82	(3R,4R)-(+)[g]
23		18:trans/cis = 2:1	trans: 94[f] cis : 95[f]	38[h]	not determined
24			—	49	

[a] Epoxidations carried out with (S,S)-4 afforded products of opposite configuration. [b] Ee's were determined by GC (see caption to Figure 1) unless otherwise noted. [c] Isolated yields correspond to reactions carried out on 1 mmol scale with 4 mol% 4 and product isolation by flash chromatography. [d] Contained with (3R,4S)-(+)-3 (ref. 9b). [e] Absolute configuration assigned by analogy to 6. [f] Ee determined by ¹H NMR using Eu(hfc)₃ as chiral shift reagent. [g] Personal communication from Drs. R. Gericke and J. Sombroek (E. Merck). [h] Isolated yield of the 2:1 mixture.

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Example 25

Example 25 was carried out the same as Example 19 above, with the exception that the catalyst shown in FIGURE 2 was used. The isolated yield was found to be 78% and the ee was 91%.

5   Example 26

Example 26 was carried out as a larger scale production of the epoxychroman produced in Example 17 above, namely 6-cyano-2,2-dimethyl-3,4-epoxychroman.

The pH of a solution of commercial household bleach (Clorox®)
10   was buffered to pH=11.3 with 0.05 M Na_2HPO_4 and 1 N NaOH and then cooled to O °C. To 500 ml of this solution (approximately 0.55 M in NaOCl) was added a 0 °C solution of 6-cyano-2,2-dimethylchromene and the catalyst (3.1 g, 5.0 mmol, 3.7 mol%) in 135 ml of CH_2Cl_2. The two-phase system was mechanically stirred at 0 °C and the reaction progress was monitored by
15   HPLC. After 9 hours, the heterogeneous brown mixture was filtered through a pad of Celite diatomaceous earth and the organic phase was separated, washed once with 500 ml saturated NaCl solution, and then dried (Na_2SO_4). The ee of the crude product obtained after solvent removal was determined for each example by GC analysis. The brown oily residue was then dissolved in
20   200 ml of boiling absolute ethanol and then water (200 ml) was added slowly to the hot solution. A hot gravity filtration afforded a pale yellow solution from which the crystallized epoxychroman was isolated. This isolated yield was 81% and the ee was measured at 99% by GC analysis.

Example 27

25   Example 27 was carried out to produce the cromakalin compound shown in Figure 13. The epoxychroman produced in Example 26, namely 6-cyano-2,2-dimethy-3,4-epoxychroman, (1g, 4.97 mmol), 3-hydroxy-1-methyl-1,6-dihydropyridazin-6-one (0.652 g, 5.17 mmol) and pyridine (0.491 g, 6.21 mmol) were refluxed together in ethanol (10 ml) for 8 hours.

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The h mogenous yellow mixture was then concentrated under vacuum and the residue was isolated by flash chromatography on 70 g of silica and ethyl acetate as eluent. The isolated yield was 1.38 g (85%).
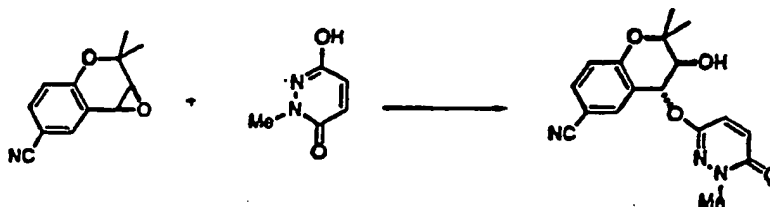
Example 28

5 Example 28 was carried out to produce the cromakalin shown in Figure 12. Sodium hydride (0.199 g of a 60% suspension in mineral oil, 4.97 mmol) was suspended in DMSO (1.5 ml) and 2-pyrrolidinone (0.423 g, 4.97 mmol) was added to the stirred mixture at room temperature under a dry nitrogen atmosphere. The epoxychroman from Example 26 (1g, 4.97 mmol)
10 was then added as a solid to the grey foamy mass. The mixture was stirred at room temperature for 10 hours. The orange-red mixture was then treated with 10 ml of water and the resulting thick yellow precipitated was extracted 5 times with 10 ml of ethyl acetate. Removal of solvent and chromatography on silica (100g, ethyl acetate eluent) afforded pure product which was
15 recrystallized from ethyl acetate. This isolated yield was 0.808 g (56%).
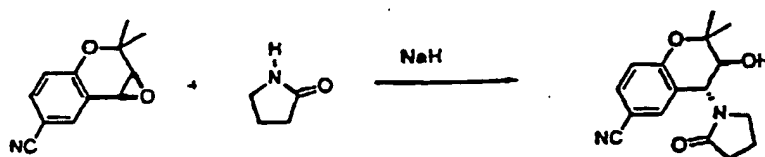
Synthesis of Taxol and Taxol Intermediates and Analogs

The following general comments apply to the following examples. Melting points were obtained in open capillary tubes with a Laboratory Devices (Holliston MA) Mel-Temp II melting point apparatus and
20 are reported uncorrected. The boiling points are reported uncorrected. The

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^{1}H NMR spectra were obtained on a General Electric (Schenectady NY) QE-300 (300 MHz) spectrometer. Low resolution EI gas chromatography/mass spectroscopic (GC/MS) analyses were performed on a Hewlett-Packard (Palo Alto CA) 5970 Mass Selective Detector coupled to a Hewlett-Packard 5890

5   gas chromatograph. Other mass spectra were provided by the Mass Spectrometry Laboratory at the University of Illinois, Urbana, Illinois. Elemental analyses were performed by the Microanalytical Laboratory of the University of Illinois.

Silica gel chromatographic purifications were performed by flash

10   chromatography with Woelm silica (Aldrich Chemical Co., Milwaukee WI) packed in 32-64 m glass columns. The weight of silica gel was approximately 50-100 times that of the sample unless it is noted otherwise below. The eluting solvent for each purification was determined by thin layer chromatography (TLC). Analytical TLC was conducted on Merck glass plates

15   coated with 0.25 mm of silica gel 60 F_{254}. TLC plates were visualized with ultraviolet light and/or in an iodine chamber unless noted otherwise. Gas-liquid chromatographic (GC) analyses were performed on a Hewlett-Packard HP 5890 gas chromatograph using the following columns: A) J&W Scientific (Folsom CA) 0.32 mm X 30 m DB-5 capillary column or B) J&W Scientific

20   CPX-B (ß-cyclodextrin) capillary column, 30 m. Optical rotations were measured on a Jasco (Japan Spectrophotometric Co., Tokyo, Japan) Dip-360 digital polarimeter.

The buffered bleach solutions employed in the epoxidation reactions were prepared from Clorox® bleach according to the method of

25   Zhang W.; and Jacobsen, EN: J. Org. Chem. 56: 2296, 1991. Unless other noted, all starting materials were purchased from Aldrich and were used as received.

Example 29

Preparation of Methyl 3-Phenylglycidate

A quantity of cis-methyl cinnamate (4.5 mg, 2.5 mmol) was dissolved in 6 ml of CH_2Cl_2. 3,5-Dimethylpyridine-N-oxide (125 mg, 40 mol%) was then added to the solution, followed by the addition of catalyst (S,S)-4 (150 mg, 10 mol%). The resulting solution was cooled to 0°C and combined with bleach solution (15 ml at a pH of 11.25) pre-cooled to 4°C. The reaction mixture was stirred at 4°C for three hours. Hexane (60 ml) was then added to the reaction mixture. The organic phase was washed once with 30 ml water and twice with 3 ml brine and dried over Na_2SO_4. Solvent was removed under vacuum and the residue was purified by chromatography (EtOAc/hexane = 7:93, v/v) to provide an inseparable mixture of cis- and trans-methyl-3-phenylglycidate in which the cis:trans ratio was 4:1. The yield was 356 mg, or 80%. The assignment of stereoisomers and determination of ratio of stereoisomers was based on the literature values for ^{1}H NMR of cis-methyl-3-phenylglycidate. Denis, J.N.; Greene, A.E.; Serra, A.A.; Luche, M.-J.: J. Org. Chem. 51: 46, 1986. The ee's of the cis- and trans-epoxides were determined to be 87-89% and 60%, respectively, by GC analysis (using column B described above).

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Example 30

Preparation of cis-Ethyl Cinnamate

Ethyl phenylpropiolate (10.8 g, 0.062 mol) was dissolved in
hexane (540 ml), followed by addition of quinoline (11.2 g) and palladium on
5   calcium carbonate (Lindlar catalyst, 3.6 g). The resulting reaction mixture
was stirred under hydrogen (1 atm) at room temperature, and the progress of
the reaction was monitored closely by GC analysis. The reaction was stopped
by displacement of the hydrogen atmosphere with nitrogen once the rate of
absorption of hydrogen was observed to decrease abruptly. The resulting
10   mixture was filtered through a pad of diatomaceous earth and the filtrate was
dried over Na_2SO_4. Solvent was removed under reduced pressure. Then the
residue was distilled under vacuum (2.5 mm Hg, at 98-100° C) to provide
10.08 g of cis-ethyl cinnamate, for a yield of nearly 95%. By GC analysis,
this product mixture was found to contain 5.7% over-reduced alkane and 3.5%
15   trans-ethyl cinnamate, but was used without further purification.

Example 31

Preparation of (2R,3R)-Ethyl-3-Phenylglycidate

With 1.76 g or 10 mmol of cis-ethyl cinnamate prepared as
described in Example 30, 4-phenylpyridine-N-oxide (420 mg, 2.5 mmol) was
20   dissolved in CH_2Cl_2 (20 ml). Catalyst (the R,R-enantiomer of Figure 8) (360
mg, 0.6 mmol) was added to the solution. This solution and the buffered
bleach solution (25 ml, at pH = 11.25) were cooled separately in ice bath, and
then combined at 4° C. The two-phase mixture was stirred for two hours, or
until the disappearance of cis-ethyl cinnamate was judged to be complete by
25   TLC analysis. Ethyl acetate (200 ml) was then added to the solution and the
organic phase was separated, washed with water (2 X 100 ml) and brine (1 X
100 ml). Then the organic phase was dried over Na_2SO_4. The solvent was
removed under vacuum and the residue was subjected to GC analysis, which
indicated the presence of cis- and trans-epoxides in a 3:1 ratio. The residue
30   was distilled (2mm Hg, at 75°-77° C) to provide 1.6g (80% yield) of a crude

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mixture of 75% cis-epoxide, 18% trans-epoxide and several minor impurities, as determined by GC analysis. The ee of the cis-epoxide was determined to be 96-97% by a ^{1}H NMR shift study with Eu(hfc)$_3$ as chiral shift reagent. The ee of the trans-epoxide was measured to be 78% by the same method. The

5   mixture was used in subsequent reactions without further purification. The following was obtained for cis-ethyl-3-phenylglycidate: ^{1}H NMR (CDCl$_3$) δ 1.02 (t, J = 7.2 Hz, 3H), 3.83 (d, J = 4.8 Hz, 1H), 3.9-4.1 (m, 2H), 4.27 (d, J = 4.8 Hz, 1H), 7.2-7.5 (aromatic, 5H). The following was obtained for trans-ethyl-3-phenylglycidate: ^{1}H NMR (CDCl$_3$) δ 1.33 (t, J = 7.2 Hz, 3H),

10   3.51 (d, J = 2.1 Hz, 1H), 4.09 (d, J = 1.8 Hz, 1H), 4.2-4.4 (m, 2H), 7.2-7.5 (aromatic, 5H).

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·Example 32

Preparation of (2R,3S)-3-Phenyl-Isoserinamide

First, 900 mg, or 4.22 mmol, of (2R,3R)-3-phenylglycidate, prepared as described in Example 31, was dissolved in a solution of 20 ml of

5   ethanol saturated with ammonia (prepared by passing ammonia through ethanol at -15° C for 15 minutes). This solution was placed in an autoclave and heated to 100° C for 16 hours with external agitation. After the solution was cooled to room temperature, agitation was continued for another eight hours. Solvent was removed under vacuum and the residue was recrystallized from

10   ethanol. White crystalline product, weighing 540 mg, was isolated by filtration for a yield of 71 %. The melting point was 172-173° C. The following ^{1}H NMR (DMSO-d$_6$/D$_2$O) data were obtained for this compound: δ 3.87 (d, J = 3.3 Hz, 1H), 4.08 (d, J = 3.3 Hz, 1H), 7.0-7.5 (aromatic, 5H). Analytical for C$_9$H$_{12}$O$_2$N$_2$: Calculated: C, 60.00; H, 6.67; N, 15.55. Found:

15   C, 59.90; H, 6.71; N, 15.25.

The corresponding racemate was synthesized by an analogous sequence with epoxide prepared with the (S,S) catalyst of Figure 8. The melting point for the racemate was 192-193° C, which compared favorably to the literature value of 187-188° C. Kamandi, E.; Frahm, A.W.; and

20   Zymalzowski, F.: Arch. Parmaz. 307: 871, 1974.

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Example 33

(2R,3S)-3-Phenyl-Isoserine

(2R,3S)-3-phenyl-isoserinamide (200 mg, 1.11 mmol), as prepared in Example 32, was combined with 354 mg (1.12 mmol) of

5    $Ba(OH)_2 \cdot 8H_2O$ and water (2 ml). The resulting suspension was heated to reflux for nine hours. After the reaction mixture was cooled to 80° C, 15 ml of water was added to the solution. The temperature of the solution was maintained at 80° C for 20 minutes before a solution of 110 mg, 1.11 mmol of concentrated sulfuric acid in 1 ml of water was added. A white precipitate

10   appeared in the solution which was determined to have a pH of between 5 and 7. Heating at 80° C was maintained for another 20 minutes, and the mixture was then cooled to room temperature. The resulting precipitate ($BaSO_4$) was centrifuged to the bottom of the container, the supernatant was separated, and solvent was removed under vacuum. The resulting white solid was extracted

15   with acetone and collected by filtration to provide 148 mg of the title compound, for a yield of 74%. The material melted with decomposition at 238°C. The ^1H NMR (D_2O/NaOD) data were as follows: δ 3.94 (d, J = 3.9 Hz, 1H), 4.01 (d, J = 3.9 Hz, 1H), 7.0-7.5 (aromatic, 5H). Analytical for $C_9H_{11}NO_3$: Calculated: C, 59.66; H, 6.07, N, 7.73. Found: C, 59.10; H,

20   6.11; N, 7.61.

Example 34

N-Benzoyl-(2R,3S)-3-Phenyl-Isoserine

First, 60 mg (0.33 mmol) of (2R,3S)-3-phenyl-isoserine, as prepared in Example 33, was dissolved in a 10% aqueous $NaHCO_3$ (8 ml).

5 The solution was cooled to 4° C and then 143 mg (1.0 mmol) of benzoyl chloride in 120 ml aqueous solution was added. This mixture was stirred for six hours at 4° C and then acidified to a pH of 1 by addition of dilute HCl solution. The resulting white precipitate was collected by filtration. The volume of the filtrate was reduced to 2 ml and a second portion of precipitate

10 was collected and combined with the first crop. This material contained both desired product and benzoic acid. The benzoic acid was removed by stirring for six hours in ether (3 ml) containing several drops of ethanol. Next, 60 mg of the resulting product was isolated as a white solid by filtration, for a yield of 70%. This compound was determined by be more than 95% pure by ^1H

15 NMR. The melting point was 177-179° C, compared to a literature value of 167-169° C. FABMS: m/e 286 ($M^+ + 1$). The ^1H NMR (DMSO-d_6) values were as follows: δ 4.37 (d, J = 4.5 Hz, 1H), 5.46 (dd, J = 8.7 Hz and 4.5 Hz, 1H), 5.3-5.7 (b, 1H), 7.2-7.6 (m, 9H), 7.84 (d, J = 7.5 Hz, 1H), 8.58 (d, J = 9.0 Hz, 1H), 12.5-13.0 (br, 1H). FABHRMS for $C_{16}H_{16}NO_4$:

20 Calculated: 286.1079. Observed: 286.1068. $[\alpha]^{25}D$-35.9° (c 0.565, EtOH); compared to literature values for the (2S,3R)-isomer of $[\alpha]^{25}D$-36.5° (c 1.45, EtOH) and for the (2R,3S)-isomer of $[\alpha]^{25}D$-37.78° (c 0.9, EtOH). Ojima I., et al. J. Org. Chem. 56: 1681, 1991.
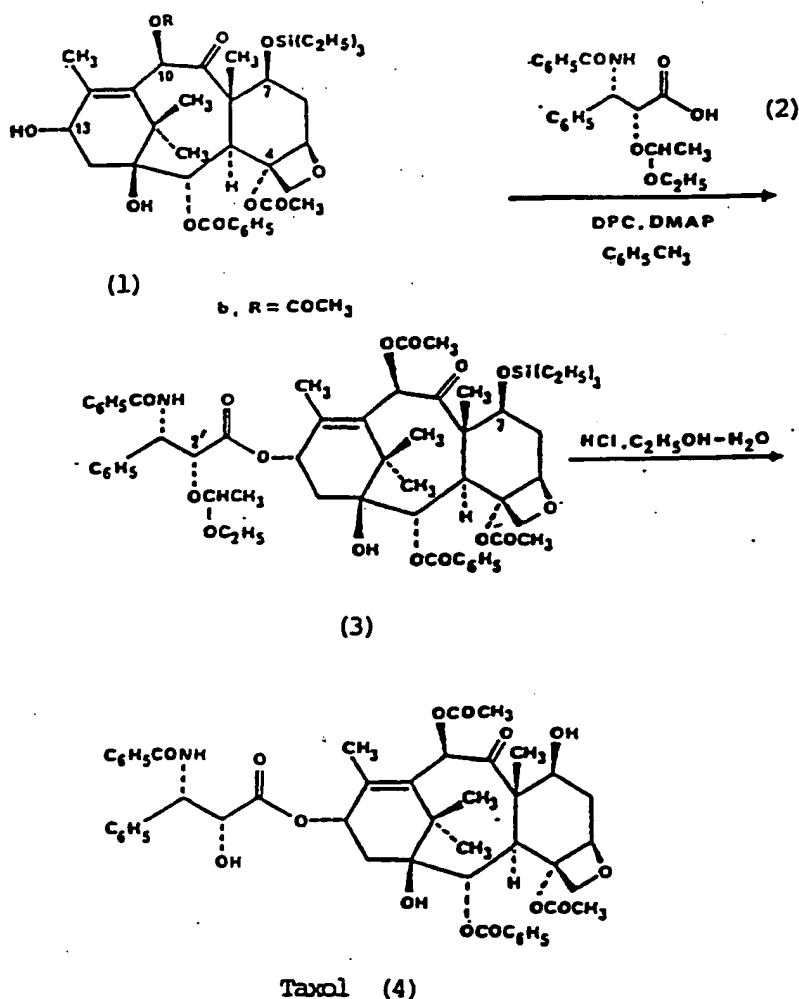
Example 35

25   Taxol

The N-benzoyl-(2R,3S)-3-phenyl-isoserine, as prepared in Example 34, is treated with 1-chloroethyl ethyl-ether in the presence of a tertiary amine to produce optically pure (2R,3S)-N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine (2). 7-tri-ethylsilyl baccatin III (1), as synthesized

30 according to Denis et al. (J. Amer. Chem. Soc. 110:5417, 1988), is added to

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6 equiv of optically pure (2R,3S)-N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-
isoserine (2), 6 equiv of di-2-pyridyl carbonate (DPC), and 2 equiv of 4-
(dimethylamino) pyridine (DMAP) in toluene solution (0.02M). This mixture
reacts at 73°C for 100 hours to produce the C-2', C-7-protected taxol
5   derivative (3).

        Concomitant removal of the protecting groups at C-2' and C-7
in (3) is accomplished with 0.5% HCl in ethanol at 0°C for 30 hours to
produce taxol, whose identity and purity are established via comparison with
the melting point, rotation, and spectral (IR, MNR, FABMS) and
10   chromatographic (TLC, HPLC) characteristics of the natural product.

(1)

b. R = COCH₃

(2)

DPC.DMAP
C₆H₅CH₃

(3)

HCl.C₂H₅OH-H₂O

Taxol (4)

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Examples 36-39

Effect Of Pyridine-N-Oxide Derivative On Epoxidation

The four alkenes shown in Table IV below were epoxidized with the presence of a pyridine-N-oxide derivative in the following manner.

5   A solution of 10 mmol of an alkene and 2.0 mmol (20 mol %) of a pyridine-N-oxide derivative were dissolved in 10 ml of CH_2Cl_2. Either 4-phenylpyridine-N-oxide (A in the table) or 4-t-butylpyridine-N-oxide (B in the table) was used.

Then, 0.08-1.0 mmol (0.8-10 mol%) of Catalyst 1 or 2 (see

10   below) were added to the alkene solution. The table shows the amounts of catalyst used in each example. This solution and buffered bleach solution (pH=11.25) were cooled separately in an ice bath and then combined at 0-4° C. This two-phase mixture was stirred for one to five hours. Then, 200 ml of hexane was added to the solution, and the organic phase was separated and

15   washed once with 100 ml water and once with 100 ml brine. The organic phase was then dried over Na_2SO_4. The solvent was removed under vacuum. The residue was subjected to purification distillation but could also be purified by chromatography or crystallization. The enantiomeric compositions of the epoxide were established by GC on a chiral capillary column and by ^{1}H NMR

20   with a chiral shift reagent (Eu(hfc)$_3$).
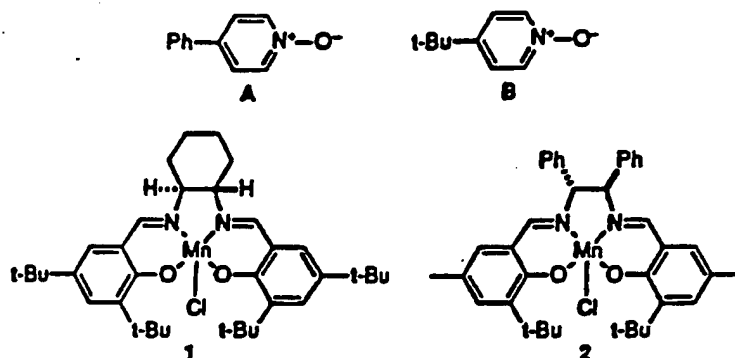
Example No.	Olefin	Major Epoxide Product	Catalyst (mol%)	N-Oxide Derivative	Isolated Yield (%)	ee (%)
36			1 (0.8)	B	70	85
37			1 (5)	A	65	88
38			2 (10)	A	50	93
39			2 (10)	A	50	93

It should be noted that, although much of the discussion has involved the use of salen derivatives (made from ethylenediamines), salpn derivatives (made from propylenediamines) and salbn derivatives (made from butylenediamines) are also within the scope of the present invention. Certainly, these are considered to lie within the scope of the invention as defined by the appended claims.

Asymmetric Oxidation of Sulfides

Example 40

The following catalysts were prepared using the same techniques as previously discussed.

Figures 19 and 20, as well as Table V below, show the generalized structures of the catalysts.

Table V

1:Y1=OMe
2:Y1=t.Bu
3:Y1=NO₂
4:Y1=H

5:Y1=OMe
6:Y1=tBU
7:Y1=Me
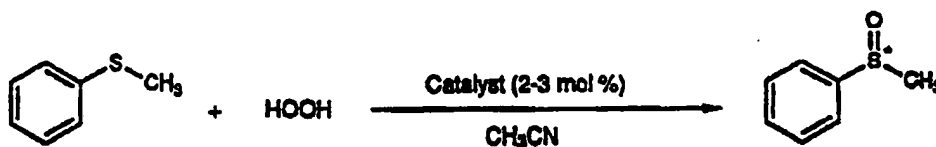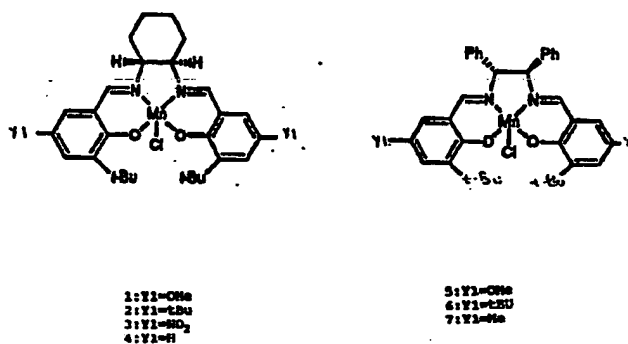
Entry	Catalyst	Yield,%[a]	ee,%[b]	Sulfoxide confign[c]
1	(R,R)-1	90	47	S-(−)
2	(R,R)-2	72	24	S-(−)
3	(R,R)-3	82	0	−
4	(R,R)-4	74	14	S-(−)
5	(R,R)-5	86	36	S-(−)
6	(R,R)-6	64	34	S-(−)
7	(R,R)-7	84	7	R-(+)

[a]All yields correspond to pure products isolated by flash chromatography. [b]Ee's were determined by HPLC using a Chiralcel OD column. [c]Absolute configuration assigned by comparison of the sign of $[\alpha]_D$ to the literature value.
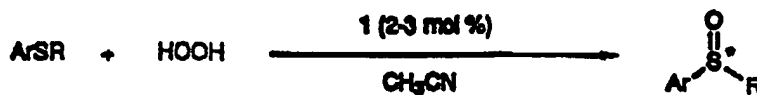
These seven catalysts were reacted with thioanisole to measure their ee values. It is significant that those ligand properties that were proven to be

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important for optimal enantioselectivity in epoxidation were also important in sulfide oxidation. For example, the presence of bulky substituents on the 3,3' and 5,5' positions of the salen ligands has a marked effect on selectivity, indicating that these groups improve stereochemical communication in the transition state leading to oxo transfer by inducing substrate approach near the dissymmetric diimine bridge. An electronic effect on enantioselectively was also very pronounced in sulfide oxidation with (salen)Mn catalysts. As exhibited in the epoxidation reaction, catalysts bearing electron withdrawing substituents are less enantioselective than electron rich analogs (entries 1, 3 and 4 in Table V). This effect may be attributed to the greater reactivity and concomitant lower selectivity, of the high valence intermediates bearing electron withdrawing groups.

Catalyst 1 of Table V emerged as the most selective of the catalysts tested. Therefore, Catalyst 1 was used to study the asymmetric oxidation of prochiral sulfides. The results of these tests are shown by Table VI below.

Asymmetric Oxidation of Prochiral Sulfides Using Catalyst (R,R)-1 or (S,S)-1.

$$\text{ArSR} + \text{HOOH} \xrightarrow[\text{CH}_3\text{CN}]{\text{1 (2-3 mol \%)}} \underset{\text{Ar}\overset{\overset{\displaystyle O}{\|}}{S}\text{R}}{}$$

| Entry	Sulfide	Catalyst	Yield (%)[a]	ee (%)[b]	Sulfoxide config[c]
1	C_6H_5–S–CH_3	(R,R)-1	90	47	S-(–)
2	o-Br-C_6H_4–S–CH_3	(R,R)-1	80	68	S-(–)
3	p-CH_3-C_6H_4–S–CH_3	(R,R)-1	95	42	S-(–)
4	C_6H_5–S–cyclopropyl	(R,R)-1	84	40	S-(–)
5	C_6H_5–S–t-C_4H_9	(R,R)-1	84	43	S-(–)
6	2-napthyl–S–CH_3	(R,R)-1	84	46	S-(–)
7	o-MeO-C_6H_4–S–CH_3	(S,S)-1	94	34	R-(+)[d]
8	p-NO_2-C_6H_4–S–CH_3	(R,R)-1	86	66	S-(–)[d]
9	m-NO_2-C_6H_4–S–CH_3	(S,S)-1	84	63	R-(+)[d]
10	p-Br-C_6H_4–S–CH_3	(S,S)-1	93	56	R-(+)[d]
11	o-I-C_6H_4–S–CH_3	(S,S)-1	95	65	R-(+)[d]

[a] Isolated yields based on sulfide. Pure sulfoxides (>99% by GC analysis) were isolated by flash chromatography.
[b] ee's were determined by HPLC using a Chiralcel OD column except for entries 8,9,10 which were determined by ^{1}H NMR in the presence of (R)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol. [c] Absolute configurations were established by comparison of the sign of $[\alpha]_D$ to literature values unless otherwise indicated. [d] Absolute configurations assigned by analogy (sign of $[\alpha]_D$) to entries 1-6.

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Selectivities in these cases were moderate, although a significant electronic effect on substrate could be discerned. More reactive electron rich sulfides were oxidized with lower selectivity (e.g. entry 7, Table VI), while selectivities above 60% ee were obtained with substrates bearing halide or

5   nitro groups (entries 2, 8-11, Table VI). The face selectivity in the sulfide oxidation reactions is analogous to that in the alkene epoxidation (see FIGURE 21). This suggests that the nature of the transition states in the two processes may be similar.

Catalytic Disproportionation of Hydrogen Peroxide

10   Example 41-Preparation of:
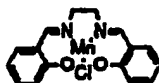
A solution of salicylaldehyde (24.42g, 0.200molc) in 80 ml of EtOh was added to a stirred solution of ethylenediamine (6.070g, 0.100,olc) in a mixture of 50 ml EtOH and 50 ml of H2O over a period of 5 minutes. The reaction mixture was refluxed for 1 hour and stirred at room temperature

15   overnight. The yellow crystalline product was separated by filtration and washed with 2 X 30 ml of cold 60% EtOh and air dried to yield 25.733G (95.9%) of salen.

Mn(OAc)2 (24.509g, 0.100 mole) was added to a stirred solution of 13.416g of salen in 1000 ml of 95% EtOH and the color

20   immediately changed from yellow to dark brown. the resulting mixture was refluxed for 3 hours. The solvent was removed by vacuum and the resulting residue was extracted with 1250 ml of hot water (60 degrees C) and filtered. Solid NaCl (58.44g, 1.000 mole) was added to the filtrate and brown precipitate formed immediately. The precipitate was collected by filtration and

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dried. The crude product was recrystallized from acetone/ether to give 9.672g
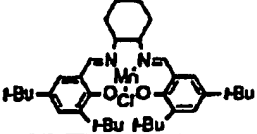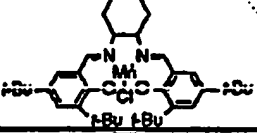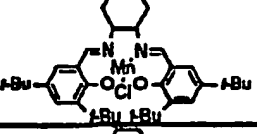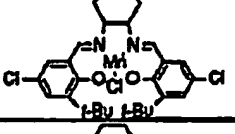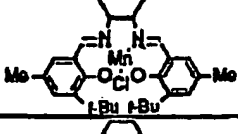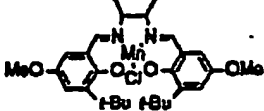of the product (54.2% yield).

Example 42-Reaction Procedure

A small round bottom flask equipped with a septum was charged
with the catalyst (0.1 mol %) and 1 ml of the solvent. To this solution was
added a buffered solution of H_2O_2. The rate and conversion of the reaction
were monitored by trapping the O_2 evolved from the reaction. Table VII
below shows the turnover values for several catalysts, whose generalized
structures are shown in FIGURES 22 and 23. Turnovers are defined as moles
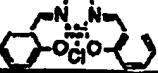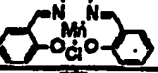of H_2O_2 destroyed per mole of catalyst.

Table VII
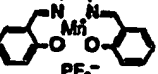
TABLE VII

Catalyst	Solvent	Turnovers
	EtOH	685
	Acetone	316
	CH₂Cl₂	804
	CH₂Cl₂	608
	CH₂Cl₂	660
	CH₂Cl₂	741

TABLE VII (Cont.)

	CH2Cl2	145
	CH2Cl2	211
	EtOH	67
	H2O	123
	H2O	153
	Et2O	38

WE CLAIM:

1.   A chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

5   where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group

10   consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

15   where at least one of R1, R2, R3 and R4 is selected from a first group consisting of hydrogen, CH3, and primary alkyls;

where, if R1 is selected from said first group, then R2 and R3 are selected from a second group consisting of aryls, secondary alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

20   where, if R2 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are selected from said second group; and

where, if R4 is selected from said first group, then R2 and R3 are selected from said second group.

2.   The catalyst of Claim 1 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os.

3.   The catalyst of Claim 1 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, and Co.

4.   The catalyst of Claim 1 wherein the metal ion is Mn.

5.   The catalyst of Claim 1 wherein said first group consists of hydrogen and methyl.

6.   The catalyst of Claim 1 wherein said first group consists of hydrogen.

7.   The catalyst of Claim 1 wherein said second group consists of t-butyl and phenyl.

8.   The catalyst of Claim 1 wherein said second group consists of phenyl.

9.   The catalyst of Claim 1 wherein R1 is the same as R3 and R2 is the same as R4.

10.   The catalyst of Claim 9 wherein said first group consists of hydrogen and methyl.

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11. The catalyst of Claim 9 wherein said second group consists f t-butyl and phenyl.

12. The catalyst of Claim 1 wherein X1 and X3 are independently selected from the group consisting of t-butyl and phenyl.

5 13. The catalyst of Claim 12 wherein X1 and X3 are the same.

14. The catalyst of Claim 1 wherein both X1 and X3 are t-butyl.

15. A chiral catalyst having the following structure:
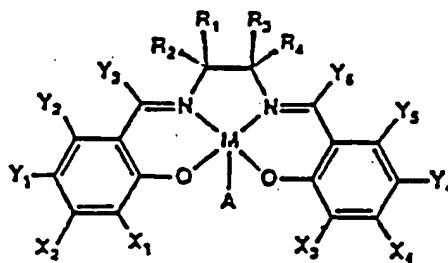
where M is a transition metal ion selected from the group consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os;

10 where A is an anion;

where X1 and X3 are the same and are selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where X2, X4, Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

where R1 and R4 are the same and are either selected from a first group consisting of H, CH_3, C_2H_5, and primary alkyls, or selected from a second group consisting of aryls, second alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

where R2 and R3 are the same and are either selected from said second group if R1 and R4 are selected from said first group, or selected from said first group if R1 and R4 are selected from said second group.
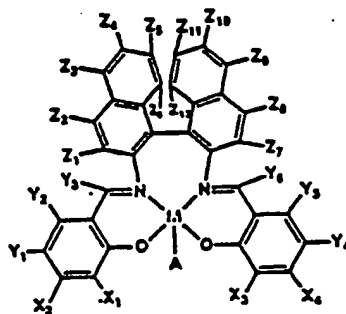
16.   The catalyst of Claim 15 wherein the metal ion is manganese.

17.   The catalyst of Claim 15 wherein said first group consists of hydrogen.

18.   The catalyst of Claim 15 wherein said second group consists of t-butyl and phenyl.

19.   The catalyst of Claim 15 wherein said second group consists of phenyl.

20.   A chiral catalyst having the following structure:

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where M is a transition metal ion;

where A is an anion;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and

5   hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; and

where Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7,

10   Z8, Z9, Z10, Z11, and Z12 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms.

21.   The catalyst of Claim 20 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os.

15   22.   The catalyst of Claim 20 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, and Co.
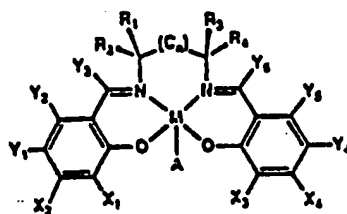
23.   The catalyst of Claim 20 wherein Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, and Z12 are hydrogen.

24.   The catalyst of Claim 20 wherein X1 and X3 are independently

20   selected from the group consisting of t-butyl and phenyl.

25.   The catalyst of Claim 20 wherein X1 and X3 are the same.

26.   A chiral catalyst having the following structure:

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where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group

consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y3 and Y6 are independently selected from the group consisting of H and primary alkyl groups;

where either one or two of R1, R2, R3 and R4 is hydrogen;

where, if R1 is hydrogen, then R3 is a primary alkyl;

where, if R2 is hydrogen, then R4 is a primary alkyl;

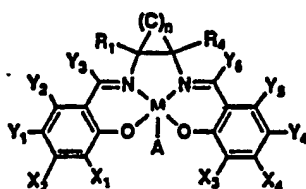where, if R3 is hydrogen, then R1 is a primary alkyl; and

where, if R4 is hydrogen, then R2 is a primary alkyl.

27.   The catalyst of Claim 26 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os.

28.   The catalyst of Claim 26 wherein the metal ion is Mn.

29.   The catalyst of Claim 26 wherein R1 is the same as R3 and R2 is the same as R4.

30.   The catalyst of Claim 26 wherein X1 and X3 are independently

5   selected from the group consisting of t-butyl and phenyl.

31.   The catalyst of Claim 30 wherein X1 and X3 are the same.

32.   The catalyst of Claim 30 wherein Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

33.   The catalyst of Claim 32 wherein Y1 and Y4 are the same.

10   34.   The catalyst of Claim 26 wherein X1, X3, Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

35.   The catalyst of Claim 34 wherein X1, X3, Y1 and Y4 are all the same.

36.   The catalyst of Claim 26 wherein X1, X3, Y1 and Y4 are all

15   t-butyl.

37.   The catalyst of Claim 26 wherein R1 and R4 are hydrogen and R2 and R3 are methyl.

38.   A chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 3, 4, 5 or 6;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y3, and Y6 are independently selected from the group consisting of hydrogen and primary alkyl groups;

where R1 and R4 are trans to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen; and

where the carbons in the $(C)_n$ portion have substituents selected from the group consisting of hydrogen, alkyl, aryl, and heteroatoms.
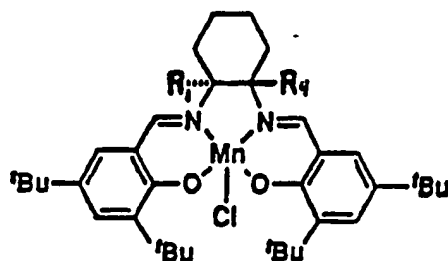

39.   The catalyst of Claim 38 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os.

40.   The catalyst of Claim 38 wherein the metal ion is Mn.

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41.   The catalyst of Claim 38 wherein R1 is the same as R4.

42.   The catalyst of Claim 38 wherein X1 and X3 are independently selected from the group consisting of t-butyl and phenyl.

43.   The catalyst of Claim 42 wherein X1 and X3 are the same.

5   44.   The catalyst of Claim 38 wherein Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

45.   The catalyst of Claim 44 wherein Y1 and Y4 are the same.

46.   The catalyst of Claim 38 wherein X1, X3, Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

10   47.   The catalyst of Claim 46 wherein X1, X3, Y1 and Y4 are all the same.

48.   The catalyst of Claim 38 wherein X1, X3, Y1 and Y4 are all t-butyl.

49.   The catalyst of Claim 48 wherein R1 and R4 are hydrogen.

15   50.   The catalyst of Claim 38 wherein R1 and R4 are selected from the group consisting of hydrogen and methyl.

51.   The catalyst of Claim 38 wherein R1 and R4 are hydrogen.

52.   The catalyst of Claim 38 wherein n is 4.

53.   A chiral catalyst having the following structure:

where R1 and R4 are _trans_ to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen.

54.   The catalyst of Claim 53 wherein the metal ion is Mn.

55.   The catalyst of Claim 53 wherein R1 is the same as R4.

56.   The catalyst of Claim 55 wherein R1 and R4 are hydrogen.

57.   The catalyst of Claim 53 wherein X1 and X3 are independently selected from the group consisting of t-butyl and phenyl.

58.   The catalyst of Claim 57 wherein X1 and X3 are the same.

59.   The catalyst of Claim 53 wherein Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

60.   The catalyst of Claim 59 wherein Y1 and Y4 are the same.

61.   The catalyst of Claim 53 wherein X1, X3, Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

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62.   The catalyst of Claim 61 wherein X1, X3, Y1 and Y4 are all the same.

63. .   The catalyst of Claim 53 wherein X1, X3, Y1 and Y4 are all t-butyl.

5   64.   The catalyst of Claim 63 wherein R1 and R4 are hydrogen.

65.   The catalyst of Claim 38 wherein R1 and R4 are selected from the group consisting of hydrogen and methyl.

66.   A method of enantioselectively epoxidizing a prochiral olefin with the use of a chiral catalyst comprising the steps of:

10   providing a prochiral olefin;

                providing an oxygen atom source;

                providing the chiral catalyst of Claim 1, 15, 20, 26, 38 or 53;
and

                reacting said olefin, said oxygen atom source, and said chiral

15   catalyst under such conditions and for such time sufficient to epoxidize said

olefin.

67.   The method of Claim 66 wherein the prochiral olefin is selected from the group consisting of monosubstituted and cis 1,2 disubstituted olefins.

68.   The method of Claim 66 wherein the prochiral olefin is a cis

20   disubstituted olefin bearing a primary substituent on one side of the double

bond and a secondary, tertiary, or aryl substituent on the other side.

69.   The method of Claim 66 wherein the olefin is selected from the

group consisting of:

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cis-ß-methylstyrene, dihydronaphthalene, 2-cyclohexenyl-1,1-

dioxolane, 2,2-dimethylchromene, styrene, and propylene.

70.   The method of Claim 66 wherein the oxygen atom source is

selected from the group consisting of: NaOCl, iodosomesitylene, NaIO$_4$,

5   NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, and

hexacyanoferrate ion.

71.   The method of Claim 66 wherein the oxygen atom source is

selected from group consisting of: NaOCl and iodosomesitylene.

72.   The method of Claim 66 wherein the oxygen atom source is

10   NaOCl.

73.   A method of enantioselectively epoxidizing a prochiral olefin

with the use of a chiral catalyst comprising the steps of:

        providing a prochiral olefin;

        providing an oxygen atom source;

15   providing a pyridine-N-oxide derivative;

        providing the chiral catalyst of Claim 1, 15, 20, 26, 38 or 53;

and

        reacting said olefin, said oxygen atom source, said pyridine-N-

oxide derivative, and said chiral catalyst under such conditions and for such

20   time sufficient to epoxidize said olefin.

74.   The method of Claim 73 wherein the prochiral olefin is selected

from the group consisting of monosubstituted and cis 1,2 disubstituted olefins.

75.   The method of Claim 73 wherein the prochiral olefin is a cis

disubstituted olefin bearing a primary substituent on one side of the double

25   bond and a secondary, tertiary, or aryl substituent on the other side.

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76.   The method of Claim 73 wherein the pyridine-N-oxide derivative is selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butylpyridine-N-oxide.

77.   The method of Claim 73 wherein the olefin is selected from the group consisting of:

cis-ß-methylstyrene, dihydronaphthalene, 2-cyclohexenyl-1,1-dioxolane, 2,2-dimethylchromene, styrene, and propylene.

78.   The method of Claim 73 wherein the oxygen atom source is selected from the group consisting of: NaOCl, iodosomesitylene, NaIO₄, NBu₄IO₄, potassium peroxymonosulfate, magnesium monoperoxyphthalate, and hexacyanoferrate ion.

79.   The method of Claim 73 wherein the oxygen atom source is selected from group consisting of: NaOCl and iodosomesitylene.

80.   The method of Claim 73 wherein the oxygen atom source is NaOCl.

81.   A method of enantioselectively epoxidizing a chromene derivative with a chiral catalyst comprising the steps of:

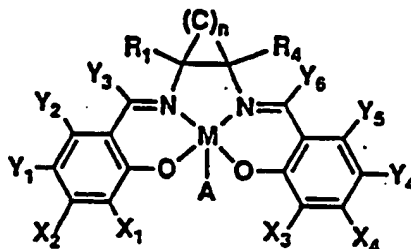providing a chromene derivative having the formula:
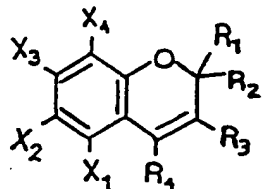
wherein R1, R2, R3, R4, X1, X2, X3 and X4 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary

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alkyls, tertiary alkyls, and hetero atoms, and wherein no more than one of R1
and R2 are hydrogen;

providing an oxygen atom source;

providing a catalyst having the formula:

where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and
hetero atoms;

where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and
hetero atoms;

where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected
from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups
bearing hetero atoms;

where at least one of R1, R2, R3 and R4 is selected from a first
group consisting of hydrogen, methyl, and primary alkyls;

where, if R1 is selected from said first group, then R2 and R3
are selected from a second group consisting of aryls, secondary alkyls, tertiary
alkyls, and alkyls bearing hetero atoms;

where, if R2 is selected from said first group, then R1 and R4
are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are
selected from said second group; and

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where, if R4 is selected from said first group, then R2 and R3 are selected from said second group; and

reacting said chromene derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said chromene derivative, to thereby produce an epoxychroman.

82. The method of Claim 81 wherein R1 and R2 on the chromene derivative are the same.

83. The method of Claim 81 wherein the R1 and R2 on the chromene derivative are alkyl groups.

84. The method of Claim 81 wherein R1 and R2 on the chromene derivative are methyl groups.

85. The method of Claim 81 wherein the chromene derivative is 6-cyano-2,2-dimethylchromene.

86. The method of Claim 81 wherein the oxygen atom source is selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$, NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

87. The method of Claim 81 wherein the oxygen atom source is NaOCl.

88. The method of Claim 81 wherein the transition metal ion is selected from the group consisting of Mn, Cr, Fe, Ni, and Co.

89. The method of Claim 81 wherein said first group consists of hydrogen and methyl.

90. The method of Claim 81 wherein said first group consists of hydrogen.

91. The method of Claim 81 wherein said second group consists of t-butyl and phenyl.

5   92. The method of Claim 81 wherein said second group consists of phenyl.

93. The method of Claim 81 wherein on the catalyst R1 is the same as R3 and R2 is the same as R4.

94. The method of Claim 81 wherein X1 and X3 on the catalyst are
10   independently selected from the group consisting of t-butyl and phenyl.

95. The method of Claim 81 wherein X1 and X3 are the same.

96. The method of Claim 81 wherein both X1 and X3 on the catalyst are t-butyl.

97. The method of Claim 81 wherein, wherein the opposite
15   enantiomer of the chiral catalyst is included to thereby produce a racemic mixture of the epoxychroman.

98. A method of enantioselectively epoxidizing a chromene derivative with a chiral catalyst comprising the steps of:
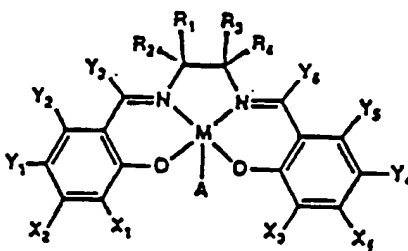   providing a chromene derivative having the formula:

- 88 -
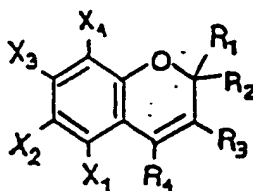
$$\begin{array}{c} X_4 \\ X_3 \quad\quad O \quad R_1 \\ \quad\quad\quad\quad R_2 \\ X_2 \quad\quad\quad R_3 \\ X_1 \quad R_4 \end{array}$$

wherein R1, R2, R3, R4, X1, X2, X3 and X4 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms, and wherein no more than one of R1

5   and R2 are hydrogen;

providing an oxygen atom source;

providing a catalyst having the formula:

$$\begin{array}{c} R_1 \quad R_3 \\ R_2 \quad\quad R_4 \\ Y_3 \quad\quad N \quad N \quad\quad Y_6 \\ Y_2 \quad\quad\quad\quad\quad\quad Y_5 \\ Y_1 \quad\quad O \quad M \quad O \quad\quad Y_4 \\ \quad\quad\quad A \\ X_2 \quad X_1 \quad\quad X_3 \quad X_4 \end{array}$$

where M is a transition metal ion selected from the group

10   consisting of Mn, Cr, Fe, Ni, Co, Ti, V, Ru, and Os;

where A is an anion;

where X1 and X3 are the same and are selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

15   where X2, X4, Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

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where R1 and R4 are the same and are either selected from a first group consisting of hydrogen, methyl, butyl and primary alkyls, or selected from a second group consisting of aryls, second alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

5   where R2 and R3 are the same and are either selected from said second group if R1 and R4 are selected from said first group, or selected from said first group if R1 and R4 are selected from said second group; and

reacting said chromene derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to
10   epoxidize said chromene derivative.

99.   The method of Claim 98 wherein R1 and R2 on the chromene derivative are the same.

100.   The method of Claim 98 wherein the R1 and R2 on the chromene derivative are alkyl groups.

15   101.   The method of Claim 98 wherein R1 and R2 on the chromene derivative are methyl groups.

102.   The method of Claim 98 wherein the chromene derivative is 6-cyano-2,2-dimethylchromene.

103.   The method of Claim 98 wherein the oxygen atom source is
20   selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$, NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

104.   The method of Claim 98 wherein the oxygen atom source is NaOCl.

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105.   The method of Claim 98 wherein the transition metal ion is manganese.

106.   The method of Claim 98 wherein said first group consists of hydrogen.

5   107.   The method of Claim 98 wherein said second group consists of t-butyl and phenyl.

108.   The method of Claim 98 wherein said second group consists of phenyl.

109.   The method of Claim 98 wherein, wherein the opposite

10   enantiomer of the chiral catalyst is included to thereby produce a racemic mixture of the epoxychroman.

110.   A method of enantioselectively epoxidizing a chromene derivative with a chiral catalyst comprising the steps of:
            providing a chromene derivative having the formula:
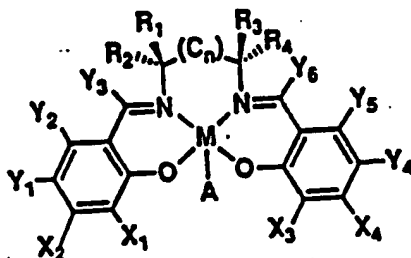

15
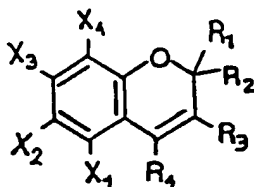
            wherein R1, R2, R3, R4, X1, X2, X3 and X4 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms, and wherein no more than one of R1 and R2 are hydrogen;

20   providing an oxygen atom source;
            providing a chiral catalyst having the formula:

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where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

5   where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and
hetero atoms;

where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and
10   hetero atoms;

where at least one of Y1 or Y2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and
hetero atoms;

where at least one of Y4 or Y5 is selected from the group
15   consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and
hetero atoms;

where Y3 and Y6 are independently selected from the group
consisting of hydrogen and primary alkyl groups;

where either one or two of R1, R2, R3 and R4 is hydrogen;

20   where, if R1 is hydrogen, then R3 is a primary alkyl;

where, if R2 is hydrogen, then R4 is a primary alkyl;

where, if R3 is hydrogen, then R1 is a primary alkyl; and

where, if R4 is hydrogen, then R2 is a primary alkyl; and

reacting said chromene derivative, said oxygen atom source, and

25   said chiral catalyst under such conditions and for such time sufficient to
epoxidize said chromene derivative, to thereby produce an epoxychroman.

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111.   The method of Claim 110 wherein R1 and R2 on the chromene derivative are the same.

112.   The method of Claim 110 wherein the R1 and R2 on the chromene derivative are alkyl groups.

5   113.   The method of Claim 110 wherein R1 and R2 on the chromene. derivative are methyl groups.

114.   The method of Claim 110 wherein the chromene derivative is 6-cyano-2,2-dimethylchromene.

115.   The method of Claim 110 wherein the oxygen atom source is

10   selected from the group consisting of NaOCl, iodosomesitylene, $NaIO_4$, NBu_4IO_4, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H_2O_2, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

116.   The method of Claim 110 wherein the oxygen atom source is NaOCl.

15   117.   The method of Claim 110 wherein the transition metal ion is manganese.

118.   The method of Claim 110 wherein for the catalyst R1 is the same as R3 and R2 is the same as R4.

119.   The method of Claim 110 wherein X1 and X3 on the catalyst are independently selected from the group consisting of t-butyl and phenyl.

20   120.   The method of Claim 119 wherein X1 and X3 on the catalyst are the same.

121.   The method of Claim 120 wherein Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

122.   The method of Claim 121 wherein Y1 and Y4 are the same.

123.   The method of Claim 122 wherein X1, X3, Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

124.   The method of Claim 123 wherein X1, X3, Y1 and Y4 are all the same.

125.   The method of Claim 124 wherein X1, X3, Y1 and Y4 are all t-butyl.

126.   The method of Claim 110 wherein on the catalyst R1 and R4 are hydrogen and R2 and R3 are methyl.

127.   The method of Claim 110 wherein the opposite enantiomer of the chiral catalyst is included to thereby produce a racemic mixture of the epoxychroman.

128.   A method of enantioselectively epoxidizing a chromene derivative with a chiral catalyst comprising the steps of:
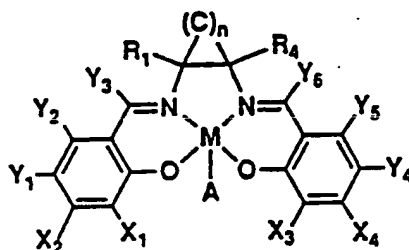   providing a chromene derivative having the formula:
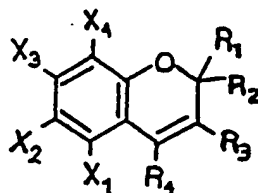
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wherein R1, R2, R3, R4, X1, X2, X3 and X4 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms, and wherein no more than one of R1 and R2 are hydrogen;

5   providing an oxygen atom source;

       providing a chiral catalyst having the formula:

       where M is a transition metal ion;

       where A is an anion;

10   where n is either 3, 4, 5 or 6;

       where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

       where at least one of X3 or X4 is selected from the group

15 consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

       where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

20   where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

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where Y3, and Y6 are independently selected from the group
consisting of hydrogen and primary alkyl groups;

where R1 and R4 are trans to each other and at least one of R1
and R4 is selected from the group consisting of primary alkyls and hydrogen;

5   and

where the carbons in the (C)$_n$ portion have substituents selected
from the group consisting of hydrogen, alkyl, aryl, and heteroatoms; and

reacting said chromene derivative, said oxygen atom source, and
said chiral catalyst under such conditions and for such time sufficient to

10   epoxidize said chromene derivative, to thereby produce an epoxychroman.

129.   The method of Claim 128 wherein R1 and R2 on the chromene
derivative are the same.

130.   The method of Claim 128 wherein the R1 and R2 on the
chromene derivative are alkyl groups.

15   131.   The method of Claim 128 wherein R1 and R2 on the chromene
derivative are methyl groups.

132.   The method of Claim 128 wherein the chromene derivative is 6-
cyano-2,2-dimethylchromene.

133.   The method of Claim 128 wherein the oxygen atom source is

20   selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$,
NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate,
H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

134.   The method of Claim 128 wherein the oxygen atom source is NaOCl.

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135.   The method of Claim 128 wherein the transition metal ion is manganese.

136.   The method of Claim 128 wherein R1 and R4 on the catalyst are the same.

5   137.   The method of Claim 128 wherein X1 and X3 on the catalyst are independently selected from the group consisting of t-butyl and phenyl.

138.   The method of Claim 137 wherein X1 and X3 on the catalyst are the same.

139.   The method of Claim 128 wherein Y1 and Y4 are independently
10   selected from the group consisting of t-butyl and phenyl.

140.   The method of Claim 139 wherein Y1 and Y4 are the same.

141.   The method of Claim 128 wherein X1, X3, Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

142.   The method of Claim 141 wherein X1, X3, Y1 and Y4 are all
15   the same.

143.   The method of Claim 128 wherein X1, X3, Y1 and Y4 are all t-butyl.

144.   The method of Claim 143 wherein R1 and R4 are hydrogen.

145.   The method of Claim 143 wherein R1 and R4 are selected from
20   the group consisting of hydrogen and methyl.

146.   The method of Claim 128 wherein R1 and R4 on the catalyst are hydrogen.

147.   The method of Claim 128 wherein n is 4.

148.   The method of Claim 128 wherein the opposite enantiomer of
5   the chiral catalyst is included to thereby produce a racemic mixture of the
epoxychroman.

149.   A method of enantioselectively epoxidizing a chromene
derivative with a chiral catalyst comprising the steps of:
    providing a chromene derivative having the formula:

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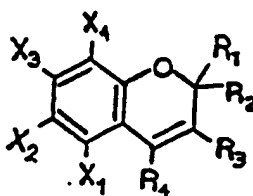
wherein R1, R2, R3, R4, X1, X2, X3 and X4 are each selected from the
group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary
alkyls, and hetero atoms, and wherein no more than one of R1 and R2 are
hydrogen;
15   providing an oxygen atom source;
    providing a chiral catalyst having the formula:
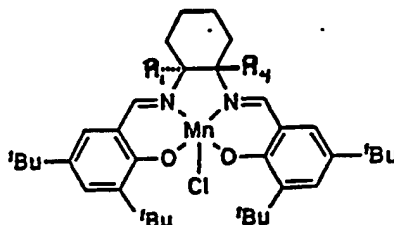
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where R1 and R4 are <u>trans</u> to each other and at least one of R1
and R4 is selected from the group consisting of primary alkyls and hydrogen;
and

reacting said chromene derivative, said oxygen atom source, and
5   said chiral catalyst under such conditions and for such time sufficient to
epoxidize said chromene derivative, to thereby produce an epoxychroman.

150.   The method of Claim 149 wherein R1 and R2 on the chromene
derivative are the same.

151.   The method of Claim 149 wherein the R1 and R2 on the
10   chromene derivative are alkyl groups.

152.   The method of Claim 149 wherein R1 and R2 on the chromene
derivative are methyl groups.

153.   The method of Claim 149 wherein the chromene derivative is 6-
cyano-2,2-dimethylchromene.

15   154.   The method of Claim 149 wherein the oxygen atom source is
selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$,
NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate,
H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

155.   The method of Claim 149 wherein the oxygen atom source is
20   NaOCl.

156.   The method of Claim 149 wherein the transition metal ion is
manganese.

157.   The method of Claim 149 wherein R1 and R4 on the catalyst are the same.

158.   The method of Claim 157 wherein R1 and R4 are hydrogen.

159.   The method of Claim 149 wherein X1 and X3 on the catalyst are independently selected from the group consisting of t-butyl and phenyl.

160.   The method of Claim 159 wherein X1 and X3 are the same.

161.   The method of Claim 149 wherein Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

162.   The method of Claim 161 wherein Y1 and Y4 are the same.

163.   The method of Claim 149 wherein X1, X3, Y1 and Y4 are independently selected from the group consisting of t-butyl and phenyl.

164.   The method of Claim 163 wherein X1, X3, Y1 and Y4 are all the same.

165.   The method of Claim 149 wherein X1, X3, Y1 and Y4 are all t-butyl.

166.   The method of Claim 165 wherein R1 and R4 are hydrogen.

167.   The method of Claim 149 wherein R1 and R4 on the catalyst are selected from the group consisting of hydrogen and methyl.

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168.   The method of Claim 149 wherein, wherein the opposite enantiomer of the chiral catalyst is included to thereby produce a racemic mixture of the epoxychroman.

169.   A method of enantioselectively epoxidizing a cis-cinnamate derivative with a chiral catalyst to produce a cis-epoxide of said cinnamate derivative, said method comprising the steps of:

providing a cis-cinnamate derivative having the formula:

wherein A1-A5 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl, alkoxy groups, F, Cl, Br, I, and amines;

wherein B1 is selected from the group consisting of unsubstituted, mono-substituted amine and di-substituted amine;

wherein G is selected from the group consisting of hydrogen, and aryls;

providing an oxygen atom source;

providing the chiral catalyst defined in claim 1, 20, 26, 38, or 53 and 5b;

reacting said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to

epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of said cinnamate derivative.

170.   The method of Claim 169 further comprising the steps of:
         providing a pyridine-N-oxide derivative;

5   and reacting said pyridine-N-oxide derivative with said cis-cinnamate, said oxygen atom source, and said chiral catalyst.

171.   The method of Claim 170 wherein said pyridine-N-oxide derivative is selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butylpyridine-N-oxide.

10   172.   The method of Claim 169 wherein the A1-A5 groups on the cis-cinnamate derivative are all the same.

173.   The method of Claim 169 wherein the A1-A5 groups on the cis-cinnamate derivative are hydrogen.

174.   The method of Claim 169 wherein R1 on the cis-cinnamate
15   derivative is an ethyl group.

175.   The method of Claim 169 wherein the cis-cinnamate derivative is cis-ethyl cinnamate.

176.   The method of Claim 169 wherein the oxygen atom source is selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$,
20   NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

177.   The method of Claim 169 wherein the oxygen atom source is NaOCl.
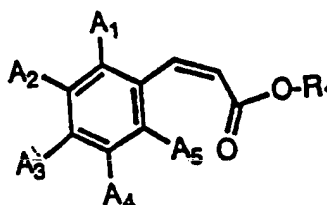
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178.   The method of Claim 169 wherein the transition metal ion is manganese.

179.   A method of making a C-13 side chain of taxol or taxol derivative, said method comprising the steps of:

5   providing a cis-cinnamate derivative having the formula:

          wherein A1-A5 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl, alkoxy, F, Cl, Br, I, and amines;

                    wherein said alkoxy is selected from the group consisting
10   of alkyls, aryls, aroyls, or alkanoyls;

          wherein R1 is an alkyl group;

          providing an oxygen atom source;

          providing the chiral catalyst defined in claim 53 or 56;

          reacting said cis-cinnamate derivative, said oxygen atom source,
15   and said chiral catalyst under such conditions and for such time sufficient to epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of said cinnamate derivative;

                    regioselectively opening said cis-epoxide of cinnamate derivative
to produce a 3-phenyl-isoserinamide derivative;

20   hydrolyzing said 3-phenyl-isoserinamide derivative to produce a
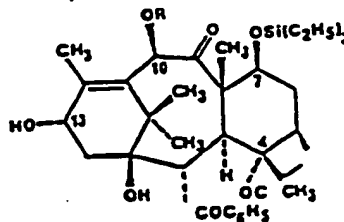3-phenyl-isoserine derivative;

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providing benzoyl chloride in sodium bicarbonate solution; and

reacting said 3-phenyl-isoserine derivative with said benzoyl chloride in sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine.

5   180.   The method of Claim 179 further comprising the steps of:

providing a pyridine-N-oxide derivative;

and reacting said pyridine-N-oxide derivative with said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst.

181.   The method of Claim 180 wherein said pyridine-N-oxide is

10   selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butyl-pyridine-N-oxide.

182.   The method of Claim 179 wherein the A1-A5 groups on the cis-cinnamate derivative are the same.

183.   The method of Claim 179 wherein the A1-A5 groups on the cis-

15   cinnamate derivative are hydrogen.

184.   The method of Claim 179 wherein R1 on the cis-cinnamate derivative is an ethyl group.

185.   The method of Claim 179 wherein the cis-cinnamate derivative is cis-ethyl cinnamate.

20   186.   The method of Claim 179 wherein the oxygen atom source is selected from the group consisting of NaOCl, iodosomesitylene, $NaIO_4$, NBu_4IO_4, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H_2O_2, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

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187.   The method of Claim 179 wherein the oxygen atom source is NaOCl.

188.   The method of Claim 179 wherein the transition metal ion is manganese.

5   189.   A method of producing taxol, said method comprising the steps of:

providing an ethyl phenylpropiolate;

partially hydrogenating ethyl phenylpropiolate to produce cis-ethyl cinnamate;

10   providing an oxygen atom source;

providing the chiral catalyst defined in claim 1, 20, 26, 38, or 53;

reacting said cis-ethyl cinnamate, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to

15   epoxidize said cis-ethyl cinnamate, to thereby produce a cis-epoxide of ethyl cinnamate;

regioselectively opening said cis-epoxide of ethyl cinnamate to produce 3-phenyl-isoserinamide;

hydrolyzing said 3-phenyl-isoserinamide to produce 3-phenyl-

20   isoserine;

providing benzoyl chloride in sodium bicarbonate solution;

reacting said 3-phenyl-isoserine with said benzoyl chloride in sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine;

reacting said N-benzoyl-3-phenyl-isoserine with 1-chloroethyl

25   ethyl ether and tertiary amine in methylene chloride to form N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine for the C13 side chain;

providing an alcohol with the formula:

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wherein R4 is a hydroxyl protecting group;

reacting, in the presence of a tertiary amine activating agent, said N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine and said alcohol to form an intermediate; and

converting the intermediate to taxol by hydrolyzing the ethoxyethyl on the C13 side chain and R4 hydroxyl protecting groups.

190.   The method of claim 189 wherein R4 is selected from ethers, esters, carbonates and silyl groups.

191.   The method of claim 189 wherein R4 is selected from ethoxyethyl, trimethyl, allyl or triethyl silyl.

192.   The method of claim 189 wherein the tertiary amine activating agent is triethyl amine, diisopropyl ethyl amine, pyridine, N-methyl imidazole, or 4-dimethylaminopyridine.

193.   The method of Claim 189 further comprising the steps of:
providing a pyridine-N-oxide derivative;
and reacting said pyridine-N-oxide derivative with said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst.

194.   The method of Claim 193 wherein said pyridine-N-oxide derivative is selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butylpyridine-N-oxide.

195.   The method of Claim 189 wherein the oxygen atom source is selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$, NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

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196.   The method of Claim 189 wherein the oxygen atom source is NaOCl.

197.   The method of Claim 189 wherein the transition metal ion is manganese.

5   198.   A method of enantioselectively oxidizing sulfides with the use of a chiral catalyst comprising the steps of:

providing a prochiral sulfide;

providing an oxygen atom source;

providing the chiral catalyst of Claim 1, 15, 20, 26, 38 or 53;

10   and

reacting said sulfide, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to oxidize said sulfide.

199.   The method of Claim 198 wherein the prochiral sulfide has the
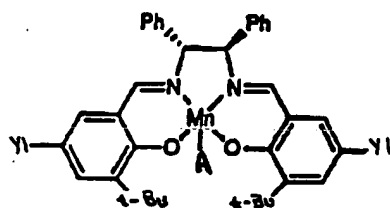15   following formula:

R1-S-R2

where R1 is any aromatic group and R2 is any alkyl group.

200.   The method of Claim 198 wherein the oxygen atom source is selected from the group consisting of hydrogen peroxide and iodosylbenzene.

20

201.   The method of Claim 198 further comprising providing a cosolvent selected from the group consisting of tetrahydrofuran, acetone and acetronitrile.

202.   A chiral catalyst having the following formula:

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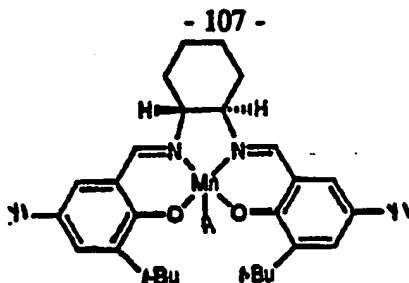
wherein Y1 is selected from the group consisting of O-CH₃, t-butyl, NO₂, and H; and

wherein A is an anion.

203.   A method of enantioselectively oxidizing a sulfide with a chiral catalyst comprising the steps of

providing a prochiral sulfide;

providing an oxygen atom source;

providing the chiral catalyst of Claim 202;

and

reacting said sulfide, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to oxidize said sulfide.

204.   The method of Claim 203 wherein the prochiral sulfide has the following formula:

R1-S-R2

where R1 is any aromatic group and R2 is any alkyl group.

205.   The method of Claim 203 wherein the oxygen atom source is selected from the group consisting of hydrogen peroxide and iododylbenzene.

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206.   The method of Claim 203 further comprising the step of providing a cosolvent selected from the group consisting of tetrahydrofuran, acetone and acetronitrile.

207.   A chiral catalyst having the following formula:

5   wherein Y1 is selected from the group consisting of O-CH$_3$, t-butyl and methyl; and

wherein A is an anion.

208.   A method of enantioselectively oxidizing a sulfide with a chiral catalyst comprising the steps of

10   providing a prochiral sulfide;

providing an oxygen atom source;

providing the chiral catalyst of Claim 207;

and

reacting said sulfide, said oxygen atom source, and said chiral

15   catalyst under such conditions and for time sufficient to oxidize said sulfide.

209.   The method of Claim 208 wherein the prochiral sulfide has the following formula:

R1-S-R2

where R1 is any aromatic group and R2 is any alkyl

20   group.

210.   The method of Claim 208 wherein the oxygen atom source is selected from the group consisting of hydrogen peroxide and iodosylbenzene.

211.   The method of Claim 208 further comprising the step of providing a cosolvent selected from the group consisting of tetrahydrofuran, acetone and acetronitrile.

212.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

providing a catalyst having the formula:
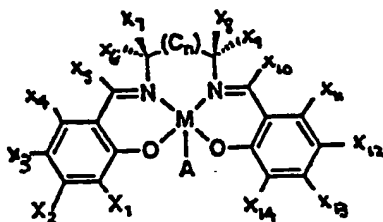
where M is a transition ion;

where A is an anion;

where n is either 0, 1, or 2;

where X1, X2, X3, X4, X5, X6, X7, X8, X9, X10, X11, X12, X13 and X14 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls and alkyl groups bearing hetero atoms;

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reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

213.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

providing the catalyst of Claim 1, 15, 20, 26, 38, 53, 202 or 203;

reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

214.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

providing a catalyst having the following formula:
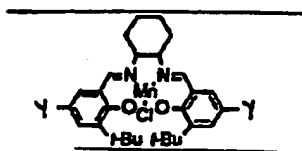
where Y is selected from the group consisting of t-butyl, Cl, methyl, and O-CH$_3$;

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reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

215.   The method of Claim 214 further comprising providing a solvent selected from the group consisting of CH_2Cl_2, EtOH, H_2O and acetone.

216.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

providing a catalyst having the formula:

reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

217.   The method of Claim 216 further comprising providing a solvent selected from the group consisting of CH_2Cl_2, EtOH, H_2O and acetone.

AMENDED CLAIMS
[received by the International Bureau on 8 February 1993 (08.02.93);
original claims 73,169,189,198 and 213 cancelled and replaced
by new claims 218-221, 229-232, 242-245, 254-257 and 261-265
respectively; claims 74-80, 170-178, 190-197 and 199-201 cancelled
and replaced by new claims 222-228, 233-241, 246-253 and 258-260
respectively; original claim 179 amended; other claims unchanged (34 pages)]

179.   A method of making a C-13 side chain of taxol or taxol
derivative, said method comprising the steps of:

providing a cis-cinnamate derivative having the formula:

5   wherein A1-A5 are each selected from the group consisting of
hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl,
alkoxy, F, Cl, Br, I, and amines;

wherein said alkoxy is selected from the group consisting
of alkyls, aryls, aroyls, or alkanoyls;

10   wherein R_1 is an alkyl group;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where R_1 and R_4 are _trans_ to each other and at least one of R_1

15   and R_4 is selected from the group consisting of primary alkyls and hydrogen;

reacting said cis-cinnamate derivative, said oxygen atom source,
and said chiral catalyst under such conditions and for such time sufficient to
epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of
said cinnamate derivative;

20   regioselectively opening said cis-epoxide of cinnamate derivative
to produce a 3-phenyl-isoserinamide derivative;

hydrolyzing said 3-phenyl-isoserinamide derivative to produce a
3-phenyl-isoserine derivative;

providing benzoyl chloride in sodium bicarbonate solution; and

reacting said 3-phenyl-isoserine derivative with said benzoyl

chloride in sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine.

5   180.   The method of Claim 179 further comprising the steps of:

providing a pyridine-N-oxide derivative;

and reacting said pyridine-N-oxide derivative with said cis-

cinnamate derivative, said oxygen atom source, and said chiral catalyst.

         181.   The method of Claim 180 wherein said pyridine-N-oxide is

10   selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butyl-

pyridine-N-oxide.

         182.   The method of Claim 179 wherein the A1-A5 groups on the cis-

cinnamate derivative are the same.

         183.   The method of Claim 179 wherein the A1-A5 groups on the cis-

15   cinnamate derivative are hydrogen.

         184. . The method of Claim 179 wherein R1 on the cis-cinnamate

derivative is an ethyl group.

         185.   The method of Claim 179 wherein the cis-cinnamate derivative

is cis-ethyl cinnamate.

20   186.   The method of Claim 179 wherein the oxygen atom source is

selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$,

NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate,

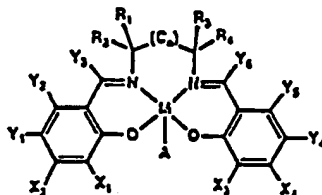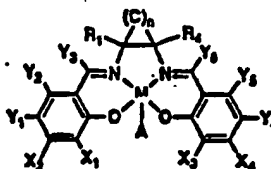H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

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218.   A method of enantioselectively epoxidizing a prochiral olefin
with the use of a chiral catalyst comprising the steps of:

    providing a prochiral olefin;

    providing an oxygen atom source;

    providing a pyridine-N-oxide derivative;

    providing a chiral catalyst having the following structure:

    where M is a transition metal ion;

    where A is an anion;

    where n is either 0, 1, or 2;

    where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

    where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

    where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected
from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups
bearing hetero atoms;

    where at least one of R1, R2, R3 and R4 is selected from a first
group consisting of hydrogen, CH$_3$, and primary alkyls;

    where, if R1 is selected from said first group, then R2 and R3
are selected from a second group consisting of aryls, secondary alkyls, tertiary
alkyls, and alkyls bearing hetero atoms;

where, if R2 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R4 is selected from said first group, then R2 and R3 are selected from said second group; and

reacting said olefin, said oxygen atom source, said pyridine-N-oxide derivative, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said olefin.

219. A method of enantioselectively epoxidizing a prochiral olefin with the use of a chiral catalyst comprising the steps of:

providing a prochiral olefin;

providing an oxygen atom source;

providing a pyridine-N-oxide derivative;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms; and

where Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7,
Z8, Z9, Z10, Z11, and Z12 are independently selected from the group
consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero
atoms; and

5   reacting said olefin, said oxygen atom source, said pyridine-N-
oxide derivative, and said chiral catalyst under such conditions and for such
time sufficient to epoxidize said olefin.

220.   A method of enantioselectively epoxidizing a prochiral olefin
with the use of a chiral catalyst comprising the steps of:

10   providing a prochiral olefin;

providing an oxygen atom source;

providing a pyridine-N-oxide derivative;

providing a chiral catalyst having the following structure:

15   where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
20   atoms;

where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where at least one of Y1 or Y2 is selected from the group
25   consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where at least one of Y4 or Y5 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where Y3 and Y6 are independently selected from the group
consisting of H and primary alkyl groups;

where either one or two of R1, R2, R3 and R4 is hydrogen;

where, if R1 is hydrogen, then R3 is a primary alkyl;

where, if R2 is hydrogen, then R4 is a primary alkyl;

where, if R3 is hydrogen, then R1 is a primary alkyl;

where, if R4 is hydrogen, then R2 is a primary alkyl; and

reacting said olefin, said oxygen atom source, said pyridine-N-
oxide derivative, and said chiral catalyst under such conditions and for such
time sufficient to epoxidize said olefin.

221.   A method of enantioselectively epoxidizing a prochiral olefin
with the use of a chiral catalyst comprising the steps of:

providing a prochiral olefin;

providing an oxygen atom source;

providing a pyridine-N-oxide derivative;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 3, 4, 5 or 6;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y3, and Y6 are independently selected from the group consisting of hydrogen and primary alkyl groups;

where R1 and R4 are _trans_ to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen;

where the carbons in the $(C)_n$ portion have substituents selected from the group consisting of hydrogen, alkyl, aryl, and heteroatoms; and

reacting said olefin, said oxygen atom source, said pyridine-N-oxide derivative, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said olefin.

222. The method of Claim 218, 219, 220 or 221 wherein the prochiral olefin is selected from the group consisting of monosubstituted and _cis_ 1,2 disubstituted olefins.

223. The method of Claim 218, 219, 220 or 221 wherein the prochiral olefin is a _cis_ disubstituted olefin bearing a primary substituent on one side of the double bond and a secondary, tertiary, or aryl substituent on the other side.

224.   The method of Claim 218, 219, 220 or 221 wherein the pyridine-N-oxide derivative is selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butylpyridine-N-oxide.

5

225.   The method of Claim 218, 219, 220 or 221 wherein the olefin is selected from the group consisting of:

cis-ß-methylstyrene, dihydronaphthalene, 2-cyclohexenyl-1,1-dioxolane, 2,2-dimethylchromene, styrene, and propylene.

226.   The method of Claim 218, 219, 220 or 221 wherein the oxygen atom source is selected from the group consisting of: NaOCl,

10   iodosomesitylene, $NaIO_4$, NBu_4IO_4, potassium peroxymonosulfate, magnesium monoperoxyphthalate, and hexacyanoferrate ion.

227.   The method of Claim 218, 219, 220 or 221 wherein the oxygen atom source is selected from group consisting of: NaOCl and iodosomesitylene.

15   228.   The method of Claim 218, 219, 220 or 221 wherein the oxygen atom source is NaOCl.

229.   A method of enantioselectively epoxidizing a cis-cinnamate derivative with a chiral catalyst to produce a cis-epoxide of said cinnamate derivative, said method comprising the steps of:

20   providing a cis-cinnamate derivative having the formula:

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wherein A1-A5 are each selected from the group consisting of
hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl,
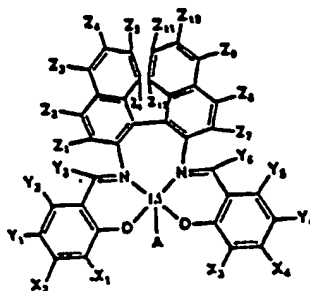alkoxy groups, F, Cl, Br, I, and amines;

wherein B1 is selected from the group consisting of
unsubstituted, mono-substituted amine and di-substituted amine;

wherein G is selected from the group consisting of hydrogen,
and aryls;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected
from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups
bearing hetero atoms;

where at least one of R1, R2, R3 and R4 is selected from a first
group consisting of hydrogen, CH_3, and primary alkyls;

where, if R1 is selected from said first group, then R2 and R3 are selected from a second group consisting of aryls, secondary alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

where, if R2 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R4 is selected from said first group, then R2 and R3 are selected from said second group; and

reacting said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of said cinnamate derivative.

230.   A method of enantioselectively epoxidizing a cis-cinnamate derivative with a chiral catalyst to produce a cis-epoxide of said cinnamate derivative, said method comprising the steps of:

providing a cis-cinnamate derivative having the formula:

wherein A1-A5 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl, alkoxy groups, F, Cl, Br, I, and amines;
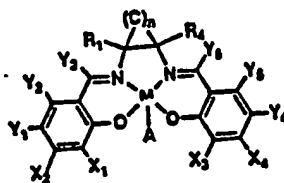
wherein B1 is selected from the group consisting of unsubstituted, mono-substituted amine and di-substituted amine;

wherein G is selected from the group consisting of hydrogen, and aryls;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, and Z12 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms; and

reacting said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of said cinnamate derivative.

231.   A method of enantioselectively epoxidizing a cis-cinnamate derivative with a chiral catalyst to produce a cis-epoxide of said cinnamate derivative, said method comprising the steps of:

providing a cis-cinnamate derivative having the formula:

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wherein A1-A5 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl, alkoxy groups, F, Cl, Br, I, and amines;

5   wherein B1 is selected from the group consisting of unsubstituted, mono-substituted amine and di-substituted amine;

wherein G is selected from the group consisting of hydrogen, and aryls;

providing an oxygen atom source;

10   providing a chiral catalyst having the following structure:
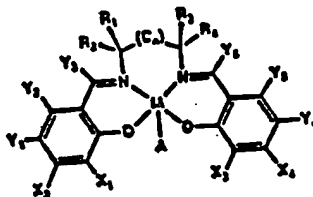
where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

15   where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero

20   atoms;

where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

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where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y3 and Y6 are independently selected from the group consisting of H and primary alkyl groups;

where either one or two of R1, R2, R3 and R4 is hydrogen;

where, if R1 is hydrogen, then R3 is a primary alkyl;

where, if R2 is hydrogen, then R4 is a primary alkyl;

where, if R3 is hydrogen, then R1 is a primary alkyl;

where, if R4 is hydrogen, then R2 is a primary alkyl; and

reacting said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of said cinnamate derivative.

232.   A method of enantioselectively epoxidizing a cis-cinnamate derivative with a chiral catalyst to produce a cis-epoxide of said cinnamate derivative, said method comprising the steps of:

providing a cis-cinnamate derivative having the formula:

wherein A1-A5 are each selected from the group consisting of hydrogen, aryls, primary alkyls, secondary alkyls, tertiary alkyls, hydroxyl, alkoxy groups, F, Cl, Br, I, and amines;

wherein B1 is selected from the group consisting of unsubstituted, mono-substituted amine and di-substituted amine;

wherein G is selected from the group consisting of hydrogen, and aryls;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 3, 4, 5 or 6;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y3, and Y6 are independently selected from the group consisting of hydrogen and primary alkyl groups;

where R1 and R4 are trans to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen;

where the carbons in the (C)n portion have substituents selected from the group consisting of hydrogen, alkyl, aryl, and heteroatoms; and

reacting said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to

epoxidize said cis-cinnamate derivative, to thereby produce a cis-epoxide of said cinnamate derivative.

233.   The method of Claim 229, 230, 231 or 232 further comprising the steps of:

providing a pyridine-N-oxide derivative;

and reacting said pyridine-N-oxide derivative with said cis-cinnamate, said oxygen atom source, and said chiral catalyst.

234.   The method of Claim 233 wherein said pyridine-N-oxide derivative is selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butylpyridine-N-oxide.

235.   The method of Claim 229, 230, 231 or 232 wherein the A1-A5 groups on the cis-cinnamate derivative are all the same.

236.   The method of Claim 229, 230, 231 or 232 wherein the A1-A5 groups on the cis-cinnamate derivative are hydrogen.

237.   The method of Claim 229, 230, 231 or 232 wherein R1 on the cis-cinnamate derivative is an ethyl group.

238.   The method of Claim 229, 230, 231 or 232 wherein the cis-cinnamate derivative is cis-ethyl cinnamate.

239.   The method of Claim 229, 230, 231 or 232 wherein the oxygen atom source is selected from the group consisting of NaOCl, iodosomesitylene, NaIO$_4$, NBu$_4$IO$_4$, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H$_2$O$_2$, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

240.   The method of Claim 229, 230, 231 or 232 wherein the oxygen atom source is NaOCl.

241.   The method of Claim 229, 230, 231 or 232 wherein the transition metal ion is manganese.

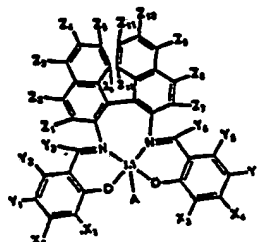5   242.   A method of producing taxol, said method comprising the steps of:

providing an ethyl phenylpropiolate;

partially hydrogenating ethyl phenylpropiolate to produce cis-ethyl cinnamate;

10   providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

15   where n is either 0, 1, or 2;

where at least one of X_1 or X_2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X_3 or X_4 is selected from the group

20   consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

where at least one of R1, R2, R3 and R4 is selected from a first group consisting of hydrogen, CH_3, and primary alkyls;

where, if R1 is selected from said first group, then R2 and R3 are selected from a second group consisting of aryls, secondary alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

where, if R2 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R4 is selected from said first group, then R2 and R3 are selected from said second group;

reacting said cis-ethyl cinnamate, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said cis-ethyl cinnamate, to thereby produce a cis-epoxide of ethyl cinnamate;

regioselectively opening said cis-epoxide of ethyl cinnamate to produce 3-phenyl-isoserinamide;
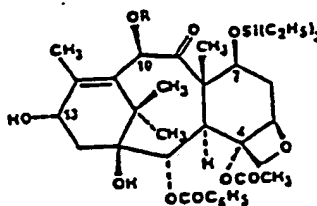
hydrolyzing said 3-phenyl-isoserinamide to produce 3-phenyl-isoserine;

providing benzoyl chloride in sodium bicarbonate solution;

reacting said 3-phenyl-isoserine with said benzoyl chloride in sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine;

reacting said N-benzoyl-3-phenyl-isoserine with 1-chloroethyl ethyl ether and tertiary amine in methylene chloride to form N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine for the C13 side chain;

providing an alcohol with the formula:

wherein R4 is a hydroxyl protecting group;

reacting, in the presence of a tertiary amine activating agent, said N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine and said alcohol to form an intermediate; and

converting the intermediate to taxol by hydrolyzing the ethoxyethyl on the C13 side chain and R4 hydroxyl protecting groups.

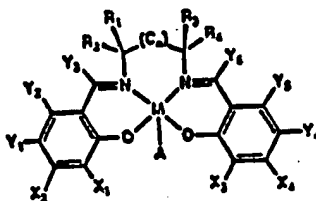243.   A method of producing taxol, said method comprising the steps of:

providing an ethyl phenylpropiolate;

partially hydrogenating ethyl phenylpropiolate to produce cis-ethyl cinnamate;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, and Z12 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

reacting said cis-ethyl cinnamate, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to epoxidize said cis-ethyl cinnamate, to thereby produce a cis-epoxide of ethyl cinnamate;

5   regioselectively opening said cis-epoxide of ethyl cinnamate to produce 3-phenyl-isoserinamide;

hydrolyzing said 3-phenyl-isoserinamide to produce 3-phenyl-isoserine;

providing benzoyl chloride in sodium bicarbonate solution;

10   reacting said 3-phenyl-isoserine with said benzoyl chloride in sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine;

reacting said N-benzoyl-3-phenyl-isoserine with 1-chloroethyl ethyl ether and tertiary amine in methylene chloride to form N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine for the C13 side chain;

15   providing an alcohol with the formula:

wherein R4 is a hydroxyl protecting group;

reacting, in the presence of a tertiary amine activating agent, said N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine and said alcohol to form

20   an intermediate; and

converting the intermediate to taxol by hydrolyzing the ethoxyethyl on the C13 side chain and R4 hydroxyl protecting groups.

244.   A method of producing taxol, said method comprising the steps of:
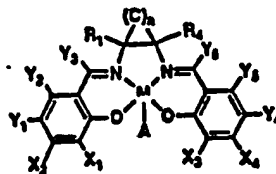
25   providing an ethyl phenylpropiolate;

partially hydrogenating ethyl phenylpropiolate to produce cis-ethyl cinnamate;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

5   where A is an anion;

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group

consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero

atoms;

10   where at least one of X3 or X4 is selected from the group

consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero

atoms;

where at least one of Y1 or Y2 is selected from the group

consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero

15   atoms;

where at least one of Y4 or Y5 is selected from the group

consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero

atoms;

where Y3 and Y6 are independently selected from the group

20   consisting of H and primary alkyl groups;

where either one or two of R1, R2, R3 and R4 is hydrogen;

where, if R1 is hydrogen, then R3 is a primary alkyl;

where, if R2 is hydrogen, then R4 is a primary alkyl;

where, if R3 is hydrogen, then R1 is a primary alkyl;

25   where, if R4 is hydrogen, then R2 is a primary alkyl;

reacting said cis-ethyl cinnamate, said oxygen atom source, and

said chiral catalyst under such conditions and for such time sufficient to

epoxidize said cis-ethyl cinnamate, to thereby produce a cis-epoxide of ethyl cinnamate;

     regioselectively opening said cis-epoxide of ethyl cinnamate to produce 3-phenyl-isoserinamide;
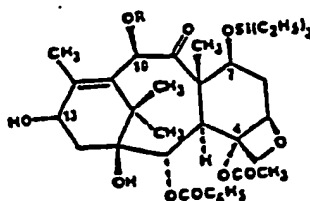
5   hydrolyzing said 3-phenyl-isoserinamide to produce 3-phenyl-isoserine;

     providing benzoyl chloride in sodium bicarbonate solution;

     reacting said 3-phenyl-isoserine with said benzoyl chloride in sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine;

10   reacting said N-benzoyl-3-phenyl-isoserine with 1-chloroethyl ethyl ether and tertiary amine in methylene chloride to form N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine for the C13 side chain;

     providing an alcohol with the formula:
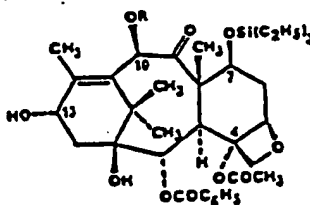
15   wherein R4 is a hydroxyl protecting group;

     reacting, in the presence of a tertiary amine activating agent, said N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine and said alcohol to form an intermediate; and

     converting the intermediate to taxol by hydrolyzing the 20   ethoxyethyl on the C13 side chain and R4 hydroxyl protecting groups.

    245.   A method of producing taxol, said method comprising the steps of:

     providing an ethyl phenylpropiolate;

     partially hydrogenating ethyl phenylpropiolate to produce cis-25   ethyl cinnamate;

     providing an oxygen atom source;

     providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 3, 4, 5 or 6;

where at least one of X1 or X2 is selected from the group.
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where at least one of Y1 or Y2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where at least one of Y4 or Y5 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

where Y3, and Y6 are independently selected from the group
consisting of hydrogen and primary alkyl groups;

where R1 and R4 are _trans_ to each other and at least one of R1
and R4 is selected from the group consisting of primary alkyls and hydrogen;

where the carbons in the (C)$_n$ portion have substituents selected
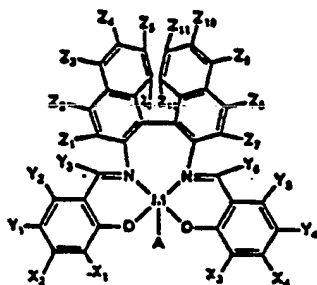from the group consisting of hydrogen, alkyl, aryl, and heteroatoms; and

reacting said cis-ethyl cinnamate, said oxygen atom source, and
said chiral catalyst under such conditions and for such time sufficient to
epoxidize said cis-ethyl cinnamate, to thereby produce a cis-epoxide of ethyl
cinnamate;

regioselectively opening said cis-epoxide of ethyl cinnamate to
produce 3-phenyl-isoserinamide;

hydrolyzing said 3-phenyl-isoserinamide to produce 3-phenyl-
isoserine;

5   providing benzoyl chloride in sodium bicarbonate solution;

reacting said 3-phenyl-isoserine with said benzoyl chloride in
sodium bicarbonate to form N-benzoyl-3-phenyl-isoserine;

reacting said N-benzoyl-3-phenyl-isoserine with 1-chloroethyl
ethyl ether and tertiary amine in methylene chloride to form N-benzoyl-O-(1-
10   ethoxyethyl)-3-phenyl-isoserine for the C13 side chain;

providing an alcohol with the formula:

wherein R4 is a hydroxyl protecting group;

reacting, in the presence of a tertiary amine activating agent,
15   said N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-isoserine and said alcohol to form
an intermediate; and

converting the intermediate to taxol by hydrolyzing the
ethoxyethyl on the C13 side chain and R4 hydroxyl protecting groups.

246.   The method of claim 242, 243, 244 or 245 wherein R4 is
20   selected from ethers, esters, carbonates and silyl groups.

247.   The method of claim 242, 243, 244 or 245 wherein R4 is
selected from ethoxyethyl, trimethyl, allyl or triethyl silyl.

248.   The method of claim 242, 243, 244 or 245 wherein the tertiary
amine activating agent is triethyl amine, diisopropyl ethyl amine, pyridine, N-
25   methyl imidazole, r 4-dimethylaminopyridine.

249. The method of Claim 242, 243, 244 or 245 further comprising the steps of:

    providing a pyridine-N-oxide derivative;

    and reacting said pyridine-N-oxide derivative with said cis-cinnamate derivative, said oxygen atom source, and said chiral catalyst.

250. The method of Claim 249 wherein said pyridine-N-oxide derivative is selected from the group consisting of 4-phenylpyridine-N-oxide and 4-t-butylpyridine-N-oxide.

251. The method of Claim 242, 243, 244 or 245 wherein the oxygen atom source is selected from the group consisting of NaOCl, iodosomesitylene, $NaIO_4$, NBu_4IO_4, potassium peroxymonosulfate, magnesium monoperoxyphthalate, H_2O_2, peroxybenzoic acid derivatives, and hexacyanoferrate ion.

252. The method of Claim 242, 243, 244 or 245 wherein the oxygen atom source is NaOCl.

253. The method of Claim 242, 243, 244 or 245 wherein the transition metal ion is manganese.

254. A method of enantioselectively oxidizing sulfides with the use of a chiral catalyst comprising the steps of:

    providing a prochiral sulfide;

    providing an oxygen atom source;

    providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

5   where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero

10   atoms;

where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

where at least one of R1, R2, R3 and R4 is selected from a first

15   group consisting of hydrogen, CH_3, and primary alkyls;

where, if R1 is selected from said first group, then R2 and R3 are selected from a second group consisting of aryls, secondary alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

where, if R2 is selected from said first group, then R1 and R4

20   are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R4 is selected from said first group, then R2 and R3 are selected from said second group; and
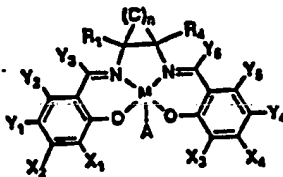
reacting said sulfide, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to oxidize said sulfide.

255.   A method of enantioselectively oxidizing sulfides with the use of a chiral catalyst comprising the steps of:

providing a prochiral sulfide;

providing an oxygen atom source;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, and Z12 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms; and

reacting said sulfide, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to oxidize said sulfide.

256.   A method of enantioselectively oxidizing sulfides with the use of
a chiral catalyst comprising the steps of:

    providing a prochiral sulfide;

    providing an oxygen atom source;

    providing a chiral catalyst having the following structure:

    where M is a transition metal ion;

    where A is an anion;

    where n is either 0, 1, or 2;

    where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

    where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

    where at least one of Y1 or Y2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

    where at least one of Y4 or Y5 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

    where Y3 and Y6 are independently selected from the group
consisting of H and primary alkyl groups;

    where either one or two of R1, R2, R3 and R4 is hydrogen;

    where, if R1 is hydrogen, then R3 is a primary alkyl;

    where, if R2 is hydrogen, then R4 is a primary alkyl;

    where, if R3 is hydrogen, then R1 is a primary alkyl;

    where, if R4 is hydrogen, then R2 is a primary alkyl; and

reacting said sulfide, said oxygen atom source, and said chiral
catalyst under such conditions and for such time sufficient to oxidize said
sulfide.

     257.   A method of enantioselectively oxidizing sulfides with the use of
a chiral catalyst comprising the steps of:

     providing a prochiral sulfide;

     providing an oxygen atom source;

     providing a chiral catalyst having the following structure:

     where M is a transition metal ion;

     where A is an anion;

     where n is either 3, 4, 5 or 6;

     where at least one of X1 or X2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

     where at least one of X3 or X4 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

     where at least one of Y1 or Y2 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

     where at least one of Y4 or Y5 is selected from the group
consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero
atoms;

     where Y3, and Y6 are independently selected from the group
consisting of hydrogen and primary alkyl groups;

where R1 and R4 are _trans_ to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen;

where the carbons in the (C)$_n$ portion have substituents selected from the group consisting of hydrogen, alkyl, aryl, and heteroatoms; and

reacting said sulfide, said oxygen atom source, and said chiral catalyst under such conditions and for such time sufficient to oxidize said sulfide.

258.   The method of Claim 254, 255, 256 or 257 wherein the prochiral sulfide has the following formula:

R1-S-R2
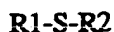
where R1 is any aromatic group and R2 is any alkyl group.

259.   The method of Claim 254, 255, 256 or 257 wherein the oxygen atom source is selected from the group consisting of hydrogen peroxide and iodosylbenzene.

260.   The method of Claim 254, 255, 256 or 257 further comprising providing a cosolvent selected from the group consisting of tetrahydrofuran, acetone and acetronitrile.

261.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

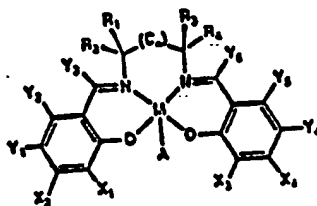providing the catalyst of Claim 202 or 203; and

reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

262.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

-141-

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

5

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group

10

consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, and Y6 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms;

15

where at least one of R1, R2, R3 and R4 is selected from a first group consisting of hydrogen, CH_3, and primary alkyls;

where, if R1 is selected from said first group, then R2 and R3 are selected from a second group consisting of aryls, secondary alkyls, tertiary alkyls, and alkyls bearing hetero atoms;

20

where, if R2 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R3 is selected from said first group, then R1 and R4 are selected from said second group;

where, if R4 is selected from said first group, then R2 and R3
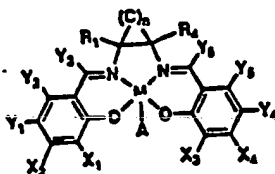
25

are selected from said second group; and

reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

263.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y1, Y2, Y3, Y4, Y5, Y6, Z1, Z2, Z3, Z4, Z5, Z6, Z7, Z8, Z9, Z10, Z11, and Z12 are independently selected from the group consisting of hydrogen, halides, alkyls, aryls, and alkyl groups bearing hetero atoms; and

reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.
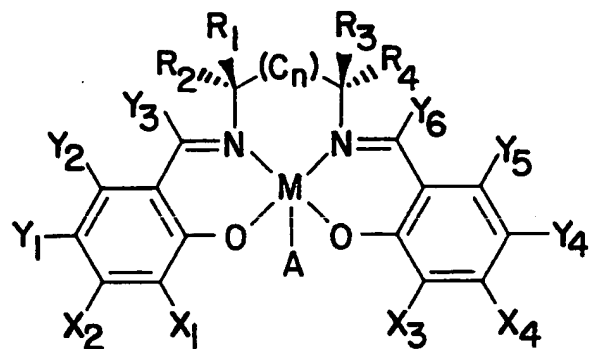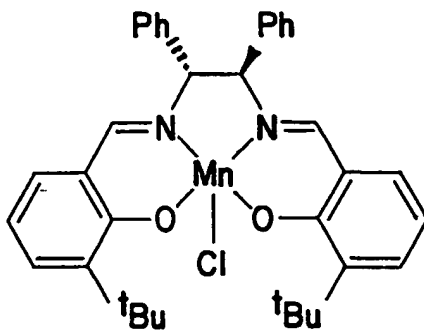
-143-

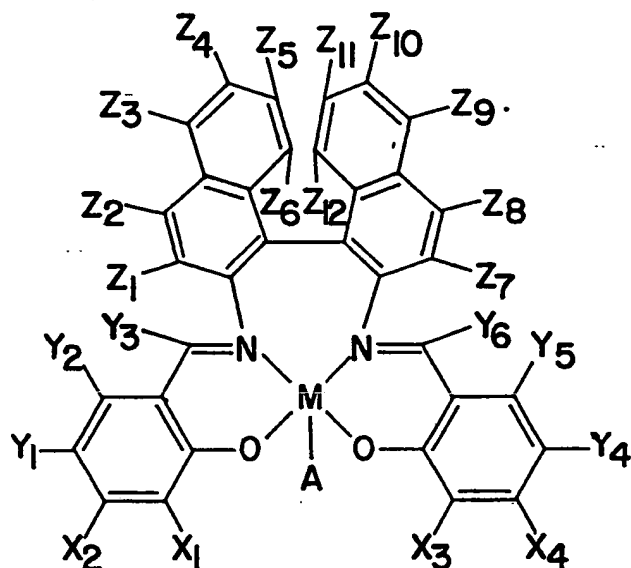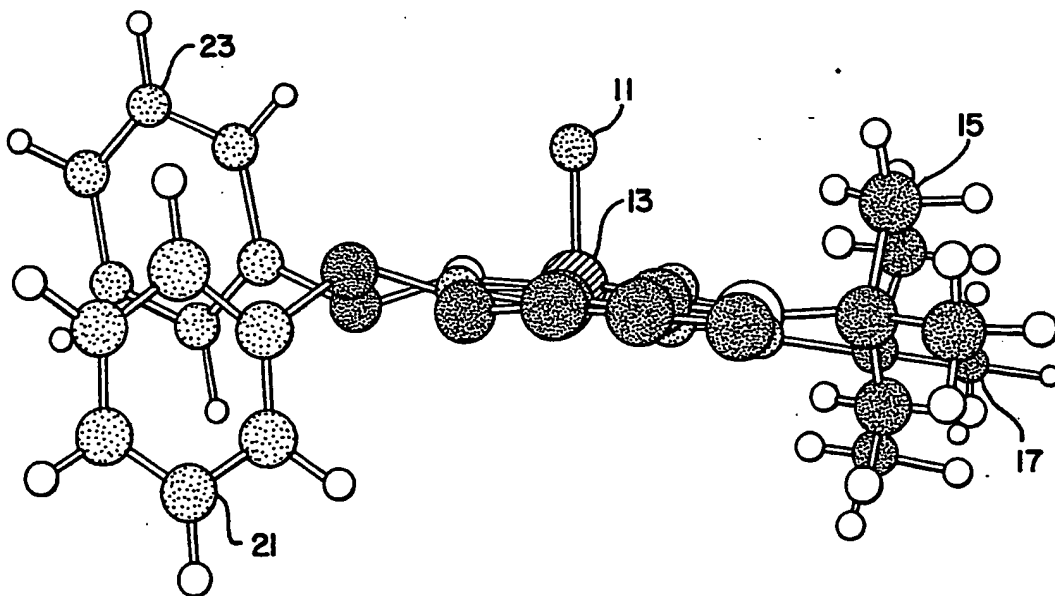264.   A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

providing hydrogen peroxide;

providing a chiral catalyst having the following structure:

where M is a transition metal ion;

where A is an anion;

where n is either 0, 1, or 2;

where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

where Y3 and Y6 are independently selected from the group consisting of H and primary alkyl groups;

where either one or two of R1, R2, R3 and R4 is hydrogen;

where, if R1 is hydrogen, then R3 is a primary alkyl;

where, if R2 is hydrogen, then R4 is a primary alkyl;

where, if R3 is hydrogen, then R1 is a primary alkyl;

where, if R4 is hydrogen, then R2 is a primary alkyl; and

reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

265. A method of catalytic disproportionation of hydrogen peroxide comprising the steps of:

   providing hydrogen peroxide;

   providing a chiral catalyst having the following structure:

   where M is a transition metal ion;

   where A is an anion;

   where n is either 3, 4, 5 or 6;

   where at least one of X1 or X2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

   where at least one of X3 or X4 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

   where at least one of Y1 or Y2 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

   where at least one of Y4 or Y5 is selected from the group consisting of aryls, primary alkyls, secondary alkyls, tertiary alkyls, and hetero atoms;

   where Y3, and Y6 are independently selected from the group consisting of hydrogen and primary alkyl groups;

where R1 and R4 are <u>trans</u> to each other and at least one of R1 and R4 is selected from the group consisting of primary alkyls and hydrogen;

where the carbons in the $(C)_n$ portion have substituents selected from the group consisting of hydrogen, alkyl, aryl, and heteroatoms; and

5   reacting said hydrogen peroxide and said catalyst under such conditions and for such time sufficient to disproportionate hydrogen peroxide to dioxygen and water.

FIG. I

FIG. 2

FIG. 3

FIG. 4

FIG. 5C

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(DISFAVORED)

FIG. 5B

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(DISFAVORED)

FIG. 5A

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(FAVORED)

FIG. 6

FIG. 7

FIG. 8

(S,S)-5   (R,R)-5
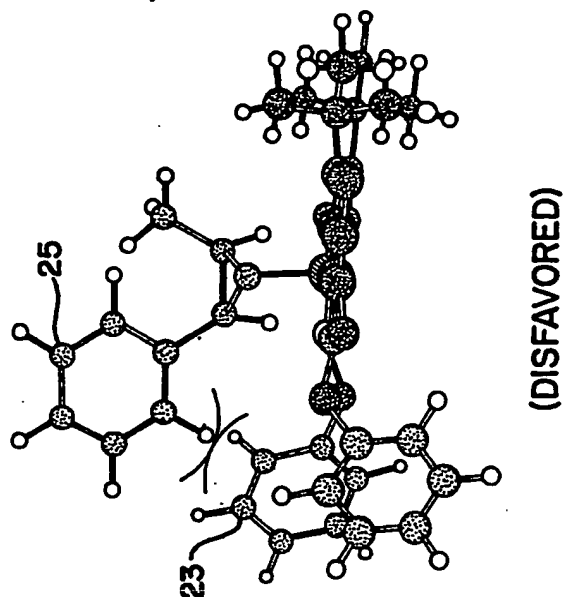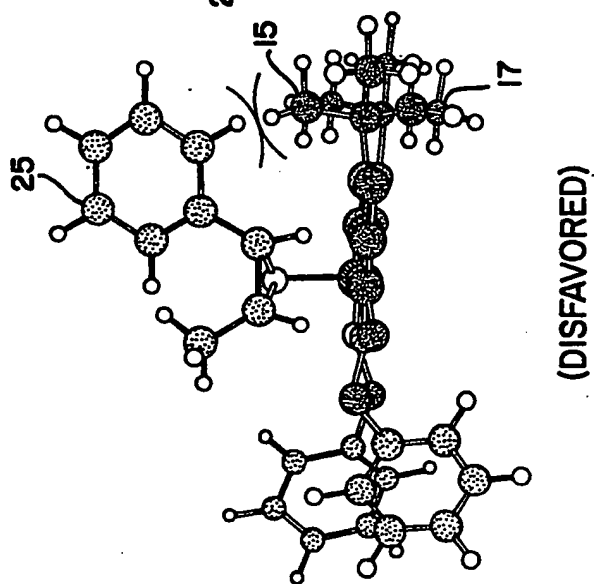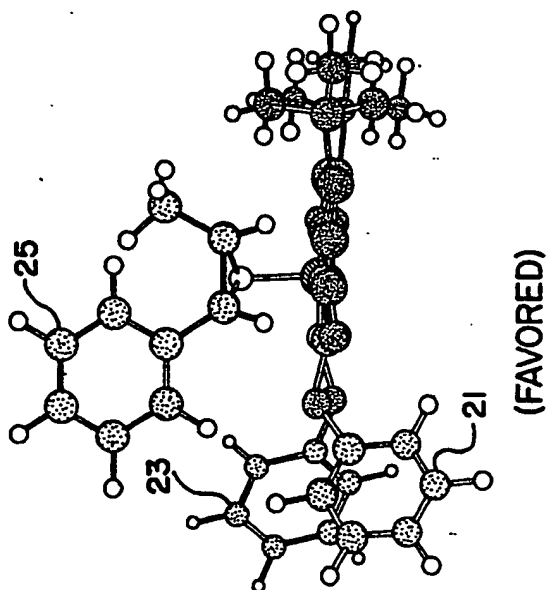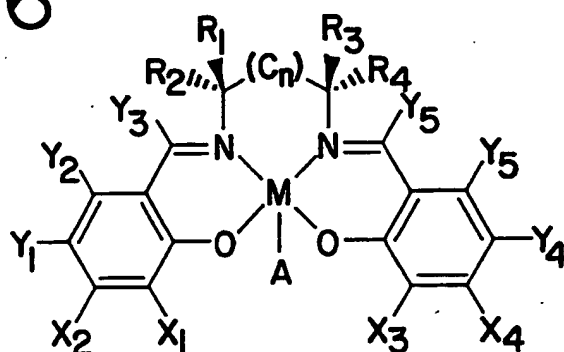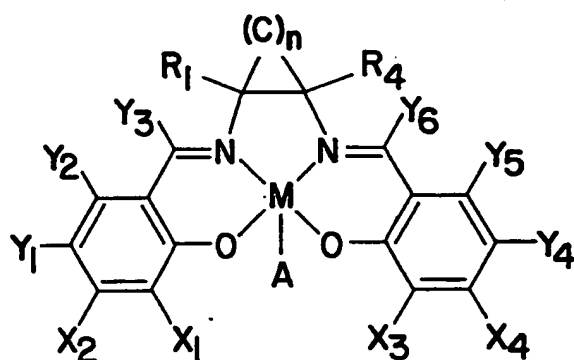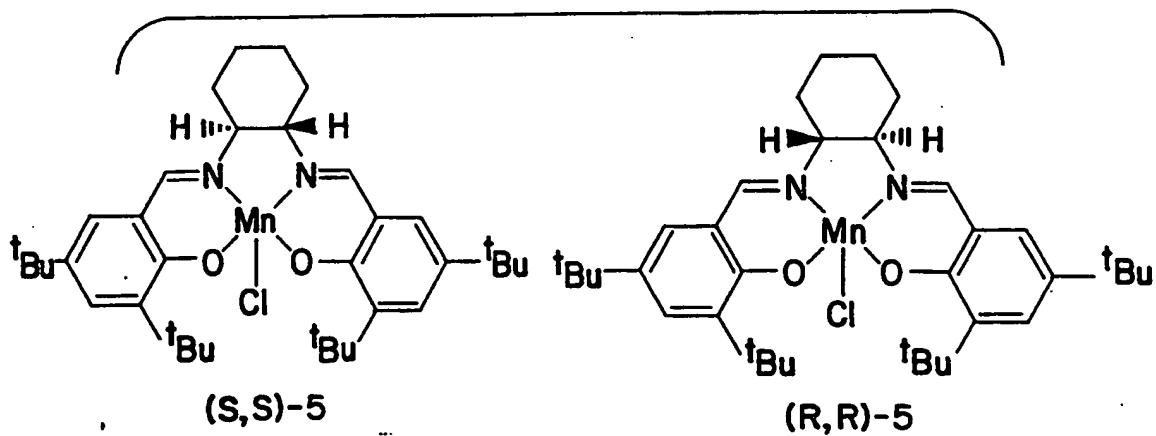
SUBSTITUTE SHEET

FIG. 9
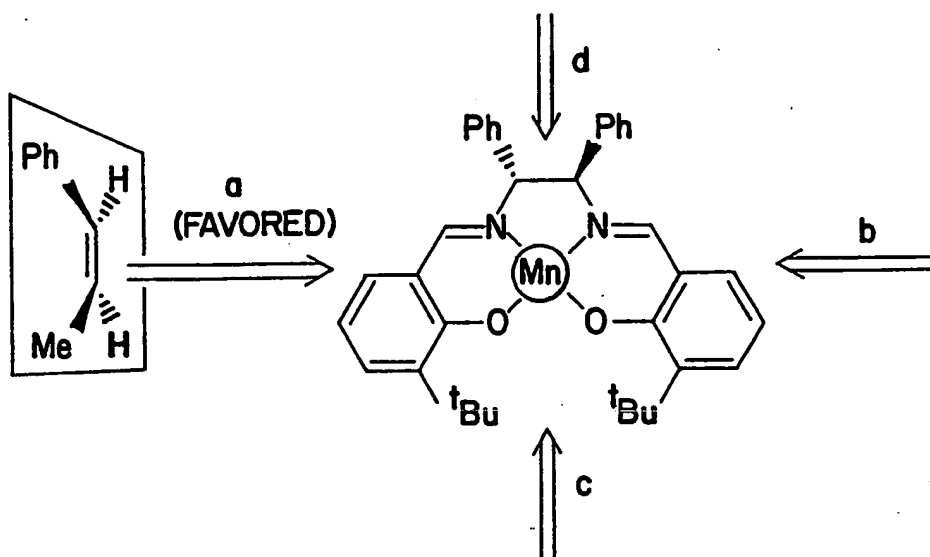
FIG. 10
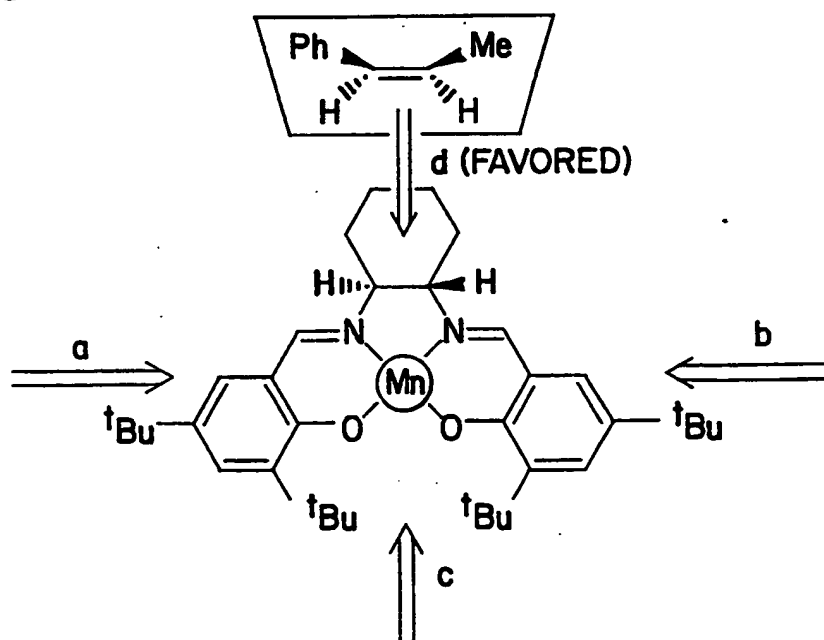
NOTE: (Mn) REPRESENTS A Mn BOND IN WHICH THE OXYGEN GROUP IS PROJECTED DIRECTLY OUT FROM THE PAGE.

FIG. II
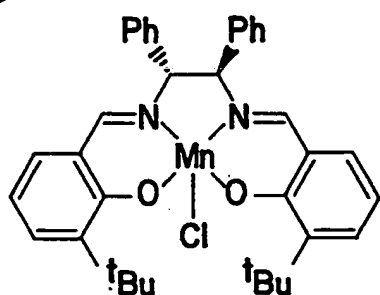
(R, R)-I
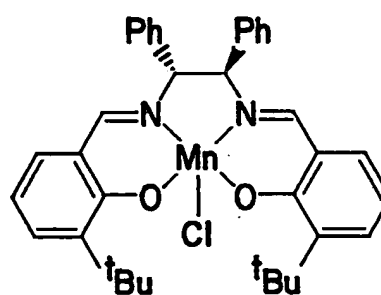
(S, S)-I
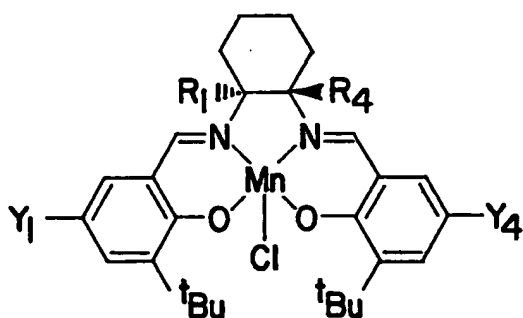
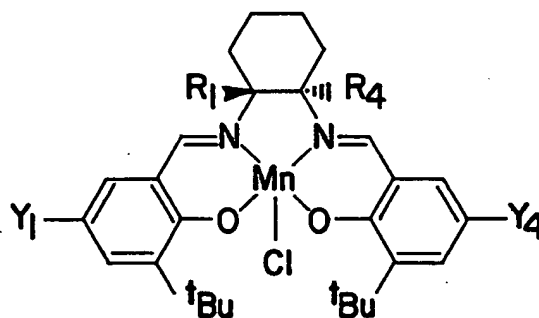(S,S)-2: $Y_1 = Y_4 = $ Me, $R_1 = R_4 = $ Me
(S,S)-3: $Y_1 = Y_4 = $ Me, $R_1 = R_4 = $ H
(S,S)-4: $Y_1 = Y_4 = $ t-Bu, $R_1 = R_4 = $ Me
(S,S)-5: $Y_1 = Y_4 = $ t-Bu, $R_1 = R_4 = $ H

(R,R)-2: $Y_1 = Y_4 = $ Me, $R_1 = R_4 = $ Me
(R,R)-3: $Y_1 = Y_4 = $ Me, $R_1 = R_4 = $ H
(R,R)-4: $Y_1 = Y_4 = $ t-Bu, $R_1 = R_4 = $ Me
(R,R)-5: $Y_1 = Y_4 = $ t-Bu, $R_1 = R_4 = $ H

FIG. 12
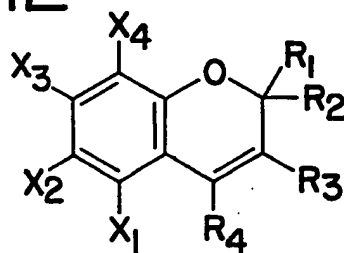
FIG. 13
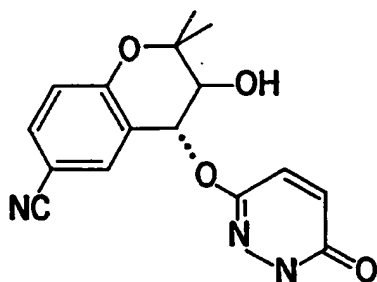
FIG. 14
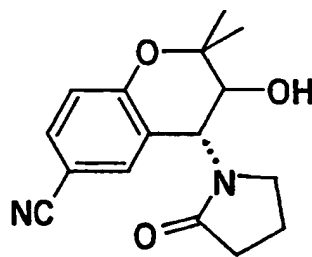
FIG. 15
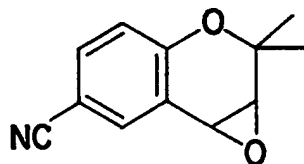
FIG. 16
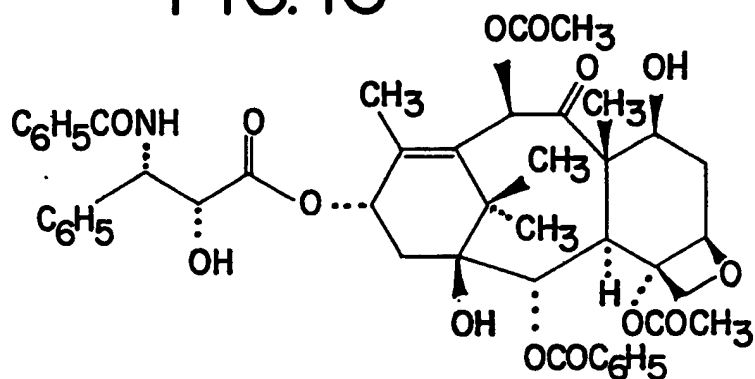
FIG. 17

FIG. 18

SUBSTITUTE SHEET

FIG. 20

5: Y_l = OMe
6: Y_l = t-Bu
7: Y_l = Me
8: Y_l = OMe
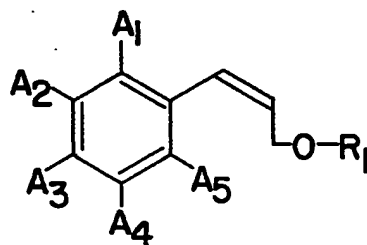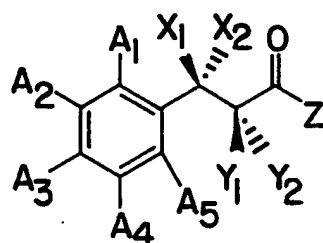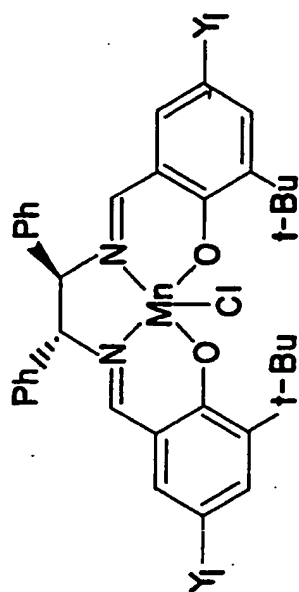
FIG. 19
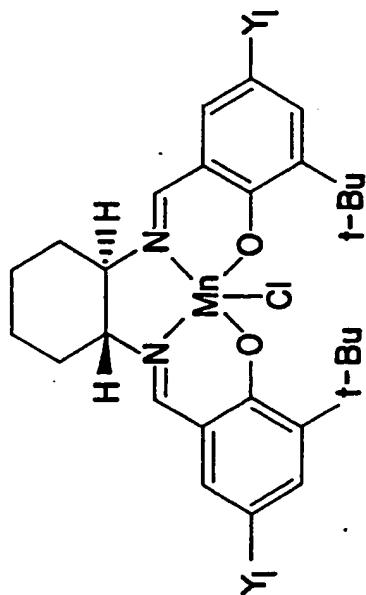
1: Y_l = OMe
2: Y_l = t-Bu
3: Y_l = NO$_2$
4: Y_l = H

FIG. 21
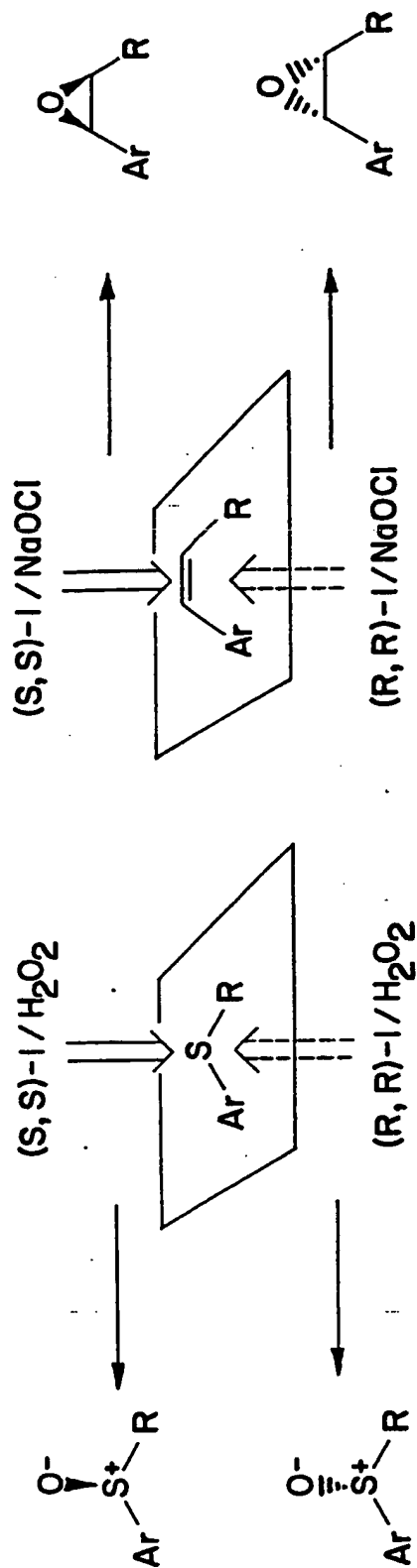
FIG. 22
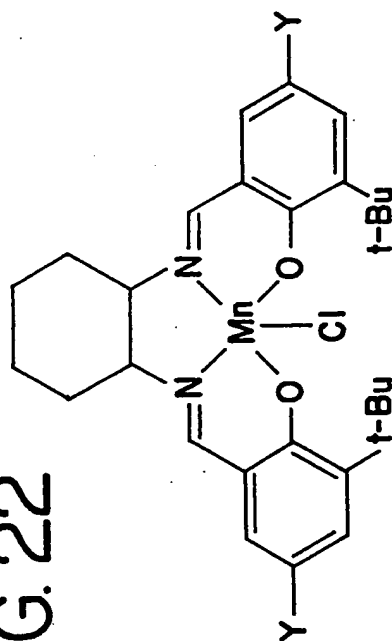
FIG. 23
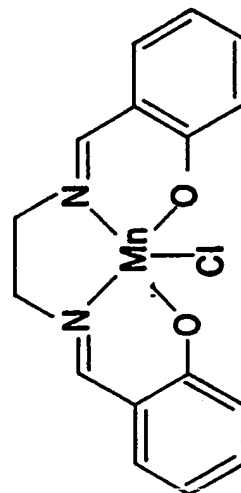
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/524, 525, 531, 533, 337, 510; 556/42, 45, 56, 57, 150, 137; 502/167; 568/27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

(1) Handbook of Chemistry and Physics, 63ᵗʰ ED, CRC Press, Inc. (1982). (2) The Merck Index, 9ᵗʰ ED, Merck & Co. Inc., 1976

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Automated Patent System (APS): taxol, isoserine, epoxychromans, catalytic disproportionation, hydrogen peroxide, sulfide oxidation reaction, manganese, chiral catalyst

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,015,744 (Holton) 14 May 1991 See entire document.	189-197
Y	Journal of American Chemical Society, Vol. 110, issued 1988 (ACS), Denis et al., "A Highly Efficient, Practical Approach to Natural Taxol", see pages 5917-5919.	189-197
Y	Tetrahedron, Vol. 46, No. 11, issued 1990 (Pergamon Press), Hönig et al., "Chemo-enzymatic synthesis of all Isomeric 3-Phenylserines and-Isoserines", see pages 3841-3850.	189-197
A		179-188

[X] Further documents are listed in the continuation of Box C.   [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 NOVEMBER 1992	07 DEC 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer _H. Leon Mecco_ PORFIRIO NAZARIO-GONZALEZ
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of American Chemical Society, Vol. 110, issued 1988 (ACS), Yoon et al., "Catalysis of Alkene Oxidation by Nickel Salen Complexes Using NaOCl under Phase-Transfer Conditions," see pages 4087-4089.	66-80
X	Journal of American Chemical Society, Vol. 112, No. 7, issued 28 March 1990 (ACS), Zhang et al. "Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by (Salen) Manganese Complexes", pages 2801-2803 see entire document.	1-19, 26-37, 66-80, 207
X	Journal of American Chemical Society, Vol. 113, No. 18, issued 28 August 1991 (ACS), Jacobsen et al., "Highly Enantioselective Epoxidation Catalysts Derived from 1,2-Diaminocyclohexane", pages 7062-4 see entire document.	1-19, 26-37, 66-80, 98-127, 169-178, 207
X	Bulletin Chemical Society of Japan, Vol. 56, No. 1, issued January 1983, Kanatomi, "The Dehydrogenation of Nickel (II) Chelates of rac- and meso- 2,2'-[(1,2-Diphenylethylene)bis(iminomethylene)diphenol and Related compounds", see pages 99-104.	1-3, 5-15, 17-19
X Y	Chemistry Letters, issued 1986 (The Chemical Society of Japan), Nakajima et al., "Asymmetric Oxidation of Sulfides to Sulfoxides by Organic Hydroperoxides with Optically Active Schiff Base - Oxovanadium (IV) Catalysts", pages 1483-6 see entire document	198-201 207-211
X	Journal of American Chemical Society, Vol. 113, No. 17, issued 14 August 1991 (ACS), Jacobsen et al., "Electronic Tuning of Asymmetric Catalysts", pages 6703-4 see entire document.	1-9, 26-37, 66-80, 97-127, 169-178 and 207
Y	US, A, 4,924,011 (Denis et al.) 08 May 1990 See entire document.	

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

B01J 31/00; C07F 9/00, 13/00, 11/00, 15/00; C07D 493/00, 301/06, 301/12, 301/14, 305/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

549/524, 525, 531, 533, 337, 510; 556/42, 45, 56, 57, 150, 137; 502/167; 568/27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/07261

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
      SEE ATTACHMENTS

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any addtional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
   Claims 1-19, 26-37, 66-201 and 203-217.

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention frist mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

   ☒ N protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

This International Searching Authority considers that the above-identified international applicati n does not comply with the requirements of unit of invention as set forth in PCT Rule 13 and 37 CFR 1.475 for the foll wing reasons:

Group I: Claims 1-19, 26-37, 66-80, 98-127, 169-178 and 207 which are drawn to the catalyst of Fig. 6 and a method for the epoxidation of a prochiral olefin using said catalyst.

Group II: Claims 38-65 and 202 which are drawn to the catalyst of Fig. 7.

Group III: Claims 20-25 which are drawn to the catalyst of Fig. 3.

Group IV: Claims 66-97 and 128-178 which are drawn to a method for the epoxidation of a prochiral olefin using the catalyst of Fig. 7.

Group V: Claims 66-80 and 169-178 which are drawn to a method for the epoxidation of a prochiral olefin using the catalyst of Fig. 3.

Group VI: Claims 179-188 which are drawn to a method of making a C-13 side chain of taxol or a taxol derivative using the catalyst of Fig. 7.

Group VII: Claims 189-197 which are drawn to a method of making taxol or a taxol derivative using the catalyst of Fig. 6.

Group VIII: Claims 189-197 which are drawn to a method of making taxol or a taxol derivative using the catalyst of Fig. 7.

Group IX: Claims 189-197 which are drawn to a method of making taxol or a taxol derivative using the catalyst of Fig. 3.

Group X: Claims 198-201 and 208-211 which are drawn to a method for the enantioselective oxidation of sulfides using the catalyst of Fig. 7.

Group XI: Claims 198-201 and 203-207 which are drawn to a method for the enantioselective oxidation of sulfides using the catalyst of Fig. 6.

Group XII: Claims 198-201 and 203-207 which are drawn to a method for the enantioselective xidation of sulfides using the catalyst of Fig. 3.

Group XIII: Claims 212-213, 216 and 217 which are drawn to a method for the catalytic disproportionation of hydrogen peroxide using the catalyst of Fig. 7.

Group XIV: Claims 213-215 which are drawn to a method for the catalytic disproportionation of hydrogen peroxide using the catalyst of Fig. 6.

Group XV: Claim 213 which is drawn to a method for the catalytic disproportionation of hydrogen peroxide using the catalyst of Fig. 3.

The claims of these groups are directed to different inventions which are not so linked as to form a single general inventive concept. For example, Groups I-III are directed to transition metal catalysts in which the tetradentate ligand is different in each group. Groups IV-V, VI, VII-IX, X-XII and XIII-XV are directed to diferent methods of using the catalysts of inventions I-III.

Please be advised that there is no right to protest for any group not paid for and that any protest must be filed no later than 15 days from the mailing of the Search Report (PCT/ISA/210). Also please note that any additional group elected (Groups II-XV) other than Group I requires a $170.00 search fee per group.